IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Tommy Ekstrom	Art Unit	: 1627
Serial No.	: 10/665,240	Examiner	: Kendra D. Carter
Filed	: September 19, 2003	Conf. No.	: 6971

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REPLY BRIEF

Appellant submits this Reply Brief in response to the Examiner's Answer dated October 27, 2011 (the Examiner's Answer), and within the two-month period for reply specified in 37 CFR § 41.41(a)(1).

I. Status of Claims

According to the Examiner's Answer at page 4, the amendment submitted July 29, 2011, was entered. This amendment canceled claims 51, 56, 67 and 68. No other amendments have been made since that date. As the status of the claims described in Appellant's Appeal Brief filed August 2, 2011 (the Appeal Brief) presumed entry of that July 29, 2011, amendment, the claims under appeal remain as listed in the Appeal Brief. To wit:

Claims 1-12, 30-33, 35, 37-41, 51, 56, 67, and 68 are canceled.

Claims 13-29, 34, 36, 42-50, 52-55, and 57-66 are rejected and under appeal.

II. Grounds of Rejection to be Reviewed on Appeal

The grounds of rejection to be reviewed on appeal are as described in the Appeal Brief on page 6, except that the provisional rejection for alleged nonstatutory obviousness-type double patenting has been withdrawn by the Examiner due to the abandonment of U.S. Application No. 09/367,950. See Examiner's Answer at page 4. That leaves only the rejections for obviousness under 35 USC § 103(a).

The Examiner's Answer did not raise a new ground of rejection.

III. Argument

Appellant and the Examiner agree that the primary reference, Carling et al., teaches use of an inhaler containing a combination of budesonide and formoterol fumarate dihydrate for treatment of asthma. There also seems to be agreement that Carling et al. recommends that the combination inhaler should be used twice per day on a regular basis: i.e., for maintenance treatment, and does not teach any other use.[1] The issues in this case thus come down to two questions: (1) whether, as the Examiner asserts, the claims encompass a situation in which the combination is administered just twice per day for maintenance treatment (i.e., as taught in Carling et al.);[2] and (2) whether, as the Examiner asserts, one of ordinary skill in the art would have believed it obvious for a patient to use the Carling et al. inhaler not only twice per day on a regular basis for maintenance treatment, but additionally one or more times per day on an irregular basis, as needed, as determined by the patient (e.g., on an emergency basis to relieve acute symptoms or when the patient expects to encounter an asthma-inducing condition).[3] Appellant has submitted evidence proving that those of ordinary skill in the art at the time of the invention believed that budesonide and other glucocorticosteroids were useless for relieving acute symptoms and potentially harmful if given in a dosage above the regular twice-daily maintenance dose, illustrating that, prior to the invention, it would have been inconceivable to prescribe a budesonide-containing inhaler for as-need use at the discretion of the patient.[4] Appellant also submitted an extraordinary amount of clinical evidence directly comparing the claimed method to the method of Carling et al., evidence that shows surprising (and highly beneficial) results obtained with the claimed method.[5] Also in the record are numerous statements by experts in the field of asthma treatment, attesting to long-felt need for an improved way to control asthma symptoms and underscoring the unexpectedness and importance to patients of Appellant's successful results.[6] Unfortunately, the Examiner continues to dismiss all of that evidence for various improper reasons (or, in some cases, no reason at all).

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1 Examiner's Answer, e.g., at pages 7 and 18.
2 *Id.*, pages 13-14.
3 *Id.*, pages 7-8.
4 Appellant's Brief on Appeal, filed August 2, 2011 ("Appeal Brief"), pages 14-25.
5 *Id.*, pages 32-40.
6 *Id.*, pages 40-43.

This Reply focuses on the following factual and legal errors found in the Examiner's Answer:

A. The Examiner has misconstrued independent claim 13 as not requiring more than the twice-per-day maintenance dose of the composition.

B. The Examiner persists in refusing to give any weight to the teaching-away evidence of record, improperly dismissing it for reasons not in accordance with the law.

C. The Examiner misinterprets Exhibit 2 as teaching the opposite of what it actually teaches.

D. The Examiner continues to give no weight to the evidence in Exhibit 3.

E. The Examiner's summary dismissal of Appellant's surprising results as "not surprising" is improper.

F. The Examiner's Answer fails to address on the merits any of the other objective evidence of nonobviousness that is of record.

Those six points are discussed in turn below.

A. The Examiner has misconstrued independent claim 13 as not requiring more than the twice-per-day maintenance dose of the composition.

Claims 13 requires administration of "(i) a maintenance dose of the composition twice per day, on a regular basis, and (ii) one or more additional doses on an irregular basis, wherein the one or more additional doses are administered as-needed, as determined by the patient." The plain reading of this portion of the claim is, of course, that the patient necessarily takes, in addition to the twice-per-day maintenance dose, at least one additional dose, with the number and timing of those additional doses determined according to the patient's own determination of need. If on a given day, the patient feels no need for an additional dose beyond the regular twice-per-day maintenance dose, and so does not take an additional dose that day, the claim does not cover his/her actions on that day. The claim covers only the method that is followed on days when the patient does feel the need for one or more additional doses, and so does administer (or is administered) those additional doses.

Despite this plain reading, the Examiner's Answer nevertheless interprets the claim as not requiring administration of any doses in addition to the maintenance dose.[7] The Examiner apparently arrives at this conclusion by reading the final clause "wherein the one or more additional doses are administered as-needed, as determined by the patient" as somehow overriding the limitation that affirmatively requires "and (ii) one or more additional doses on an irregular basis" :

> The method steps comprise administering the above composition in a maintenance dose twice per day on a regular basis and one or more additional doses on an irregular basis as-needed as determined by the patient. The clam limitation "as-needed" reads on zero to as many as the patient needs to administer the composition to treat asthma. Therefore the claim reads on a minimum of the patient taking the maintenance dose and not taking any more doses because it was not needed. With the limitation "as needed" addressed, Carling et al. obviously teaches claim 13.[8]

This mistaken interpretation of the claim permeates the Examiner's Answer. See, for example, the statement at the bottom of page 16: "Further, if the patient did not need the additional administration, the prior art clearly reads on the claimed invention," and again at the bottom of page 18: "[Even] if no additional dose was needed Carling et al. still reads on the claims."

Appellant points out that the clause of claim 13 specifying "as-needed" merely describes the conditions under which the required "one or more additional doses" are administered. It does not in any way contradict the language that explicitly requires one or more additional doses. Nor does it somehow permit "zero" additional doses as an alternative to "one or more additional doses." If a given patient on a given day does not need even one additional dose (besides the twice-daily maintenance dose), and so does not take any additional doses on that day, *then the method of treatment followed by the patient on that day is not encompassed by the claim.* The claim is infringed only on the days when the patient is administered both the maintenance dose and the specified one or more additional doses. This is clear from the unambiguous language of the claim. Appellant submits that the Examiner's above-quoted interpretation of claim 13 (saying the claim "reads on a minimum of the patient taking the maintenance dose and not taking any more doses because it was not needed") is plainly incorrect. It follows that the assertion of

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[7] Examiner's Answer, pages 13-14. See also the Examiner's arguments made in reliance on this interpretation of the claim on pages 16-17, 18, and 20 of the Examiner's Answer.

[8] Examiner's Answer, pages 13-14 (underlining in original).

obviousness that rests upon that misinterpretation ("With the limitation 'as needed' addressed, Carling et al. obviously teaches claim 13") is likewise incorrect. Reversal of the rejection of claim 13 is therefore respectfully requested.

The Examiner's Answer does not say whether the same rationale for obviousness over Carling et al. is meant to apply to any of the other independent claims. Independent claims 36, 42 and 49 all contain the same language as in claim 13 requiring that both a twice-daily maintenance dose and at least one additional dose be administered: i.e., "(i) a maintenance dose of the composition twice per day, on a regular basis, and (ii) one or more additional doses on an irregular basis." (These claims all vary in the language that follows the quoted text and describes the circumstance under which the one or more additional doses are administered.) The corresponding part of independent claim 50 is worded somewhat differently: "(i) a maintenance dose of the composition on a regular basis as determined by the patient's physician, and (ii) one or more additional doses on an irregular basis." It is incontrovertible that all of the claims affirmatively require administration of at least one dose on an irregular basis, in addition to the maintenance dose that is administered on a regular basis. Thus, to the extent that the rejection of any of the claims derives from the Examiner's misinterpretation of the scope of the claim as reading on zero additional doses, the rejection is improper and should be reversed.

B. The Examiner persists in refusing to give any weight to the teaching-away evidence of record, improperly dismissing it for reasons not in accordance with the law.

Exhibit 1 attached to the Appeal Brief is a 1997 prior art product insert for the Pulmicort® Turbuhaler® inhaler containing budesonide as the sole active ingredient. The relevant teachings of this document are discussed in detail in the Appeal Brief,[9] so will be only summarized here. Briefly, Exhibit 1 *teaches away* from the presently claimed methods by making it clear that the glucocorticosteroid budesonide (one of the two active ingredients specified in the presently claimed methods) is useful solely for regular maintenance treatment, and should be given just twice per day, in exactly the dose prescribed by the physician—never

[9] Appeal Brief, pages 14-18.

more frequently. Exhibit 1 states that the budesonide product is not useful in episodes of acute asthma attack, and furthermore can be harmful when taken more often than in the prescribed twice-daily maintenance treatment.[10] This illustrates that those of skill in the art prior to the present invention (even long after the 1993 publication date of Carling et al.) realized that a budesonide-containing composition would not be appropriate for use in other than a regular maintenance context, at a set dose every day that is never increased or decreased except under the tight control of the physician. For emergency use to relieve an acute attack or when a patient is about to encounter conditions (such as exercise or a smoky room) likely to trigger an acute attack, the patient was told to inhale as needed from a different sort of inhaler containing a short-acting bronchodilator (such as terbutaline) designed to provide immediate symptom relief. These emergency inhalers did not contain glucocorticosteroids or other potent active ingredients that were considered worthless in an emergency and also potentially dangerous if administered too frequently or in too high a dose. There would have been no point in including glucocorticosteroids in emergency inhalers, and ample reasons not to do so.[11] Appellant submits that Exhibit 1 is therefore highly relevant as a *teaching-away* from the presently claimed methods.

Rather than recognize this fact, or alternatively address Appellant's teaching-away argument on the merits, the Examiner's Answer simply dismisses Exhibit 1 as irrelevant.[12] According to the Examiner, the focus of Exhibit 1 on budesonide alone means that Exhibit 1 is "not a true comparison" with the claimed methods (which specify a combination of budesonide and formoterol), so can be ignored.[13] No legal authority for taking such a position is cited.

Appellant argued in the Appeal Brief,[14] and continues to maintain, that the Examiner's position is not a valid ground for dismissing any *teaching away* evidence. Any prior art that would have led the skilled artisan in a direction different from that taken by the inventors is

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10 *Id.*, page 16.
11 *Id.*, page 17.
12 Examiner's Answer, page 15.
13 *Id.*
14 Appeal Brief, pages 17-18.

highly relevant to the question of obviousness.[15] Exhibit 1 illustrates that those of ordinary skill in the art understood that budesonide was worthless for emergency use and potentially harmful when given more frequently than the standard twice-daily maintenance dose, so would never have been prescribed for as-needed use at the discretion of the patient, particularly where short-acting bronchodilator inhalers that don't have this perceived disadvantage were widely available for emergency use. This is true regardless of whether the budesonide is the sole active ingredient or is formulated in combination with another drug such as the long-acting bronchodilator, formoterol. When Exhibit 1 is given proper weight, the nonobviousness of the presently claimed methods is clear.

C. The Examiner misinterprets Exhibit 2 as teaching the opposite of what it actually teaches.

Exhibit 2 is a non-prior art 2001 product insert for Symbicort® Turbuhaler®, an inhaler containing a budesonide/formoterol combination (the same combination as in the present claims) for use in regular maintenance treatment.[16] This document says that the physician (not the patient) should be the one to make any adjustments in dosage, and warns that if the patient ever exceeds the prescribed maintenance dosage "medical attention must be sought."[17] This warning to seek medical attention if the prescribed dosage is exceeded illustrates that those of skill in the art *even years after Carling et al. was published* understood that a budesonide/formoterol combination is solely for use in a regular (twice daily) maintenance regimen.[18] However, the Examiner incongruously interprets this plain warning against additional doses "as verification that patients will take more than the current dose if needed."[19] The Examiner's Answer goes on to argue, "[The] insert obviously addresses the patients that use [] the medication 'as needed', thus proving that patients will use the medication 'as needed' even though it is not

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[15] *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006) ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference or would be led in a direction divergent form the path that was taken by the applicant.")

[16] Appeal Brief, pages 19-22.

[17] *Id.*, page 19.

[18] *Id.*, pages 19-21.

[19] Examiner's Answer, page 16 (emphasis omitted).

recommended."[20] This interpretation of Exhibit 2 appears to derive from the Examiner's unsupported assumption that the patient would reach for the budesonide/formoterol inhaler, rather than a short-acting β_2-agonist bronchodilator inhaler, when "faced with not breathing."[21] The Examiner's apparent assumption fails to take into account the fact that appropriate short-acting β_2-agonist bronchodilator inhalers were widely available and routinely prescribed for as-needed use, and that patients were instructed to use the short-acting β_2-agonist bronchodilator inhaler and never to use the budesonide/formoterol inhaler when "faced with not breathing." See, for example, the "Guidelines for the Diagnosis and Management of Asthma," Expert Panel Report 2, Clinical Practice Guidelines, NIH Publication No. 97-4051, July 1997, pages 57-94, previously submitted in an Information Disclosure Statement on April 6, 2009 (the "NIH Treatment Guidelines"); a copy is attached to the present Evidence Appendix as Exhibit 15. The figure at pages 84-85 of the NIH Treatment Guidelines describes a stepwise approach to asthma treatment, with the four steps corresponding to increasing severity and/or frequency of symptoms. In all four steps, a short-acting β_2-agonist is prescribed for rapid symptom relief in emergency situations (see center column), while corticosteroids[22] and long-acting bronchodilators[23], if utilized at all, are utilized solely for long-term control, i.e., regular maintenance treatment (see left column). Thus, an asthma patient "faced with not breathing" would know to inhale from a short-acting β_2-agonist inhaler, and not from an inhaler containing budesonide and formoterol.

In sum, the Examiner appears to be alleging that Exhibit 2's unambiguous warning against taking even a single extra dose actually supports the obviousness of taking extra doses whenever the patient determines there is a need, despite the stated risk of harm and the existence of better options. Appellant asks the Board to assess the teachings of Exhibit 2 independently from the Examiner's misguided interpretation, so that the warning is taken as a reason not to do something, and not as an indication it would be obvious to do it.

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[20] *Id.*
[21] *Id.*
[22] Such as budesonide
[23] Such as formoterol fumarate dihydrate

D. <u>The Examiner continues to give no weight to the evidence in Exhibit 3.</u>

Exhibit 3 is a product insert for Advair Diskus, an inhaler containing a different inhalable composition: fluticasone propionate (a glucocortiosteroid) and salmeterol (a long-acting bronchodilator). As discussed in detail in the Appeal Brief, Exhibit 3 was submitted as further evidence that those of skill in the art, even years after the priority date, understood that compositions containing glucocorticosteroids in general were not appropriate for use in other than a regular maintenance regimen, with extra doses strictly forbidden.[24] The Examiner's Answer responds by reasserting the Examiner's interpretation of Carling et al. and stating,

> Different compounds have different properties and as evidenced by Carling et al. the combination of two known compounds can also possess different properties and characteristics. In order to truly compare the two compositions of Exhibit 3 and the claimed combination both compounds need to be present.[25]

Appellant maintains that the mere fact that different compounds and combinations <u>can</u> have different properties does not mean that the point Appellant is making with Exhibit 3 is not a valid point. The evidence of record shows that those of skill in the art believed, even years after the priority date, that compositions containing glucocorticosteroids in general (whether fluticasone propionate, as in Exhibit 3, or budesonide, as in Exhibits 1 and 2) were not appropriate for use in other than a regular maintenance regimen, with extra doses strictly forbidden. Appellant asks the Board to give proper weight to Appellant's voluminous evidence on this point.

E. <u>The Examiner's summary dismissal of Appellant's surprising results as "not surprising" or "not persuasive" is improper.</u>

The Appeal Brief provided extensive evidence establishing that the presently claimed methods produce results that those of skill in the art deem highly unexpected.[26] First, Exhibit 4 reports the results of a clinical trial comparing (1) use of a budesonide/formoterol combination inhaler in the method of the invention (i.e., maintenance treatment <u>plus</u> as-needed, as determined by the patient, to relieve acute asthma symptoms), to (2) use of the same combination inhaler in the method taught by Carling et al. (i.e., maintenance treatment only, with a second inhaler

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[24] Appeal Brief, pages 22-23.
[25] Examiner's Answer, page 17.
[26] Appeal Brief, pages 32-40.

containing the standard short-acting bronchodilator terbutaline for emergency use as-needed to relieve acute asthma symptoms).[27] The method of the invention proved to be far more effective in reducing the number of acute attacks (a measure of enormous importance to any asthma sufferer) than did the method taught by Carling et al.[28] Similar striking differences were seen in many other measures described in Exhibit 4.[29] A physician not involved in the trial wrote an editorial (Exhibit 5) extolling these "surprisingly good results,"[30] thereby removing any possibility of doubt that this is how those of skill in the art viewed the results.

Although the Examiner claims to have considered the evidence of Exhibits 4 and 5, she offers her own (surprising) opinion that "the Applicant's results are not viewed as surprising."[31] The Examiner cites Carling et al.'s disclosure of certain advantages of the twice-daily maintenance treatment method disclosed in Carling et al. as being the reason that the further advantages of the presently claimed method described in Exhibit 4 "are not viewed as surprising." [32] According to the Examiner, "The combination of Carling et al. provides suitable daily doses for asthma, but does not completely eliminate a patient taking more than two administrations a day."[33]

Appellant submits that this is an entirely inadequate response to Appellant's robust evidence of highly surprising results observed when the method of the invention was directly compared to the prior art method of Carling et al., particularly given the Exhibit 5 editorial's independent confirmation that the Exhibit 4 results were "surprisingly good." The Examiner fails to explain why Carling et al.'s disclosure of advantages of Carling et al.'s method would render the further (and dramatic) advantages observed with the presently claimed method "obvious." Appellant respectfully asks the Board to give careful consideration to the Exhibit 4 and 5 evidence of surprising results, which should be more than sufficient to overcome the rejection.

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27 *Id.*, pages 32-34.
28 *Id.*, pages 32-33.
29 *Id.*, page 33.
30 *Id.*
31 Examiner's Answer, page 18.
32 *Id.*
33 *Id.* (emphasis in original).

In addition to the evidence from Exhibits 4 and 5, the Appeal Brief supplied four more exhibits (Exhibits 7-10) demonstrating further evidence of surprising results.[34] Rather than give this evidence appropriate consideration, the Examiner's Answer categorically dismisses some of these results as "not persuasive" for reasons that are not in accordance with the law,[35] and blithely ignores the rest.

For example, Exhibit 7 (Kuna et al.) showed that even doubling the amount of the maintenance dose of budesonide/formoterol given in accordance with Carling et al.'s method did not reduce severe exacerbations (acute asthma attacks) as effectively as did a lower total dose of budesonide/ formoterol given in accordance with the claimed methods.[36] The Examiner's Answer says this evidence is "not persuasive" because the abstract of Kuna et al. says that, for certain measures other than number of severe exacerbations, both treatments were equivalent, and further that both treatments were "well tolerated."[37] Thus, the Examiner seems to take the position that, in order to qualify as "persuasive," Appellant's evidence must show a surprising benefit in every parameter studied, including how well the treatments were "tolerated." This is clearly contrary to law.[38]

Exhibit 8 (Rabe et al.) is not addressed at all in the Examiner's Answer. The evidence of surprising results reported in this publication is discussed in considerable detail in the Appeal Brief at pages 37-39. See in particular the startling observation regarding efficacy of the claimed method that is set out in italics on page 38. It is unclear whether the Examiner even considered this evidence.

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[34] Appeal Brief, pages 34-39.
[35] Examiner's Answer, page 20.
[36] Appeal Brief, pages 34-35.
[37] Examiner's Answer, page 20. As pointed out in the Appeal Brief footnote 3 on page 38, the Kuna et al. abstract actually says nothing about whether the treatments are "well tolerated."
[38] *In re May*, 574 F.2d 1082 (CCPA 1978) (Evidence that the compound used in the claimed method had an unexpected property was sufficient to overcome the obviousness rejection even though the compound also had another property that was expected), and *In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective on weeds in corn and soybean crops than was the closest prior art compound was sufficient to overcome the obviousness rejection, even though the claimed compound was only an average performer on crops other than corn and soybean).

Also submitted as evidence of surprising results are Exhibit 9 (Scicchitano et al.) and Exhibit 10 (Bousquet et al.). The Examiner's Answer mentions Bousquet et al. briefly, but neglects to given any reason why the Examiner did not find it persuasive. [39] With respect to Scicchitano et al., the Examiner's Answer acknowledges this reference shows that "adjustable maintenance dosing [i.e., in accordance with the claimed methods] is more effective," but dismisses the significance of this observation solely because the reference "also teaches that both the fixed [i.e., the Carling et al. treatment] and adjustable dosing treatments were equally well tolerated."[40] Appellant is at a loss as to why the Examiner believes the latter fact to have any significance whatsoever. "Equally well tolerated" simply means that the treatments were equivalent in not causing undue discomfort or side effects—it says nothing about relative efficacy, and certainly does not neutralize the surprisingly better effectiveness observed for the presently claimed method compared to the Carling et al. method.[41] Though this point about "equally well tolerated" was explained in the Appeal Brief,[42] the Examiner's Answer does not even take note of this explanation, much less rebut it.

And finally, the Examiner offers a further reason as to why all of the surprising results were "not persuasive":

> The Examiner would still like to point out that the Carling et al. method still effectively treats asthma, and discloses that the combination provides better results than the individual medications alone.[43]

Appellant submits that the fact that Carling et al.'s prior art method "effectively treats asthma" and is better than other prior art treatments is not even close to being the point. There is no requirement under U.S. law obliging an applicant to establish that the prior art is nonfunctional in order to establish nonobviousness.[44] Further, whether the Carling et al. combination provides

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39 Examiner's Answer, page 20.
40 *Id.*
41 Appeal Brief, page 38.
42 *Id.*
43 Examiner's Answer, page 20.
44 *United States v. Adams*, 383 U.S. 39 (1966) (Battery was held nonobvious over prior art batteries that functioned but did not have the surprising advantages of the claimed battery).

"better results than the individual medications alone" is entirely irrelevant to whether the presently claimed methods of using the combination are nonobvious over Carling et al.'s method of using the combination. Appellant has shown, based on multiple clinical studies in real patients, that the presently claimed method works *better* than Carling et al.'s method by a number of important parameters, even where the total average daily dose of budesonide/formoterol administered in accordance with the present claims is *lower* than the daily dose given in accordance with Carling et al.'s method. This is classic evidence of surprising results, exactly the sort of evidence that courts and the U.S. Patent and Trademark Office routinely rely upon to find nonobviousness.

F. <u>The Examiner's Answer fails to address on the merits any of the other objective evidence of nonobviousness that is of record.</u>

In addition to the evidence of surprising results discussed above, the Appeal Brief points to several published comments illustrating that experts in the field of asthma treatment regarded the presently claimed methods as being surprising--and even *paradigm-changing*. See, for example, the detailed discussion of certain passages from the Exhibit 5 editorial (Barnes) provided on page 24 of the Appeal Brief, including a passage that illustrates why one of ordinary skill in the art would <u>not</u> have thought to use Carling et al.'s combination inhaler on an as-needed basis, and another passage characterizing the method of the invention as leading to "**changes in the paradigm of asthma management**." Similarly, Exhibit 6 (D'Urzo) states with respect to "**the recent landmark trial by O'Byrne**" (i.e., the trial reported in Exhibit 4) that "**The use of a single inhaler (budesonide/formoterol) for both maintenance and reliever therapy represents a <u>significant paradigm shift</u> in asthma management that is simple and effective.**"[45] D'Urzo says that the method is "**a novel strategy**" and praises it as "**one of the most important advances in asthma management in many years.**"[46] (This is, of course, some

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[45] Appeal Brief, page 25 (emphasis added).
[46] *Id.*

13 years after Carling et al.'s publication supposedly made the method "obvious.") Further comments by Barnes and D'Urzo and also by Scicchitano et al. (Exhibit 9) reveal the *long-felt, unsatisfied need* in the art for a more effective treatment for asthma, a need that each of these authors opines has been met by treatment in accordance with the presently claimed methods.[47]

Rather than address these experts' comments fully and on the merits, the Examiner's Answer says only that "[the] Examiner has considered the comments made by Barnes, O'Byrne et al. and D'Urzo, but does not find that the evidence overcomes the prior art for the reasons stated above and below."[48] (The Examiner's Answer does not even purport to have considered Scicchitano et al.'s comments.) Appellant can find no "reasons stated above and below" that address the Barnes and D'Urzo comments. Rather, the Examiner's Answer merely restates the Examiner's conclusory opinions: that Appellant's results "are not viewed as surprising;" that Carling et al. teaches the usefulness of a budesonide/formoterol combination for treating asthma and does not "completely eliminate a patient taking more than two administrations a day;" that "if no additional dose is needed Carling et al., still reads on the claims;"[49] and that Exhibit 2 "verifies that patients will take more than the current dose of the combination therapy if needed."[50] The Examiner gives no clue as to why she believes her subjective opinions are legally defensible in the face of contrary objective evidence of how experts in the field actually viewed the presently claimed methods.

CONCLUSION

For the reasons set forth above, Appellant respectfully requests that the rejections of claims 13-29, 34, 36, 42-50, 52-55, and 57-66 be reversed.

An Evidence Appendix listing Exhibit 15 ("Guidelines for the Diagnosis and Management of Asthma," Expert Panel Report 2, Clinical Practice Guidelines, NIH Publication No. 97-4051, July 1997, pages 57-94) is attached. This reference was originally cited in this case in an Information Disclosure Statement filed April 6, 2009.

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[47] *Id.*, pages 40-43.
[48] Examiner's Answer, page 18.
[49] *Id.*, page 18. As discussed above in section A, this assertion about what "reads on the claims" is flatly wrong, as the claims require administration of at least one additional dose.
[50] *Id.*, pages 18-19. See Appellant's rebuttal of this point regarding Exhibit 2 in section C above.

It is believed that no fees are due. Please apply any necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-0188002.

Respectfully submitted,

Date: December 27, 2011

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Evidence Appendix

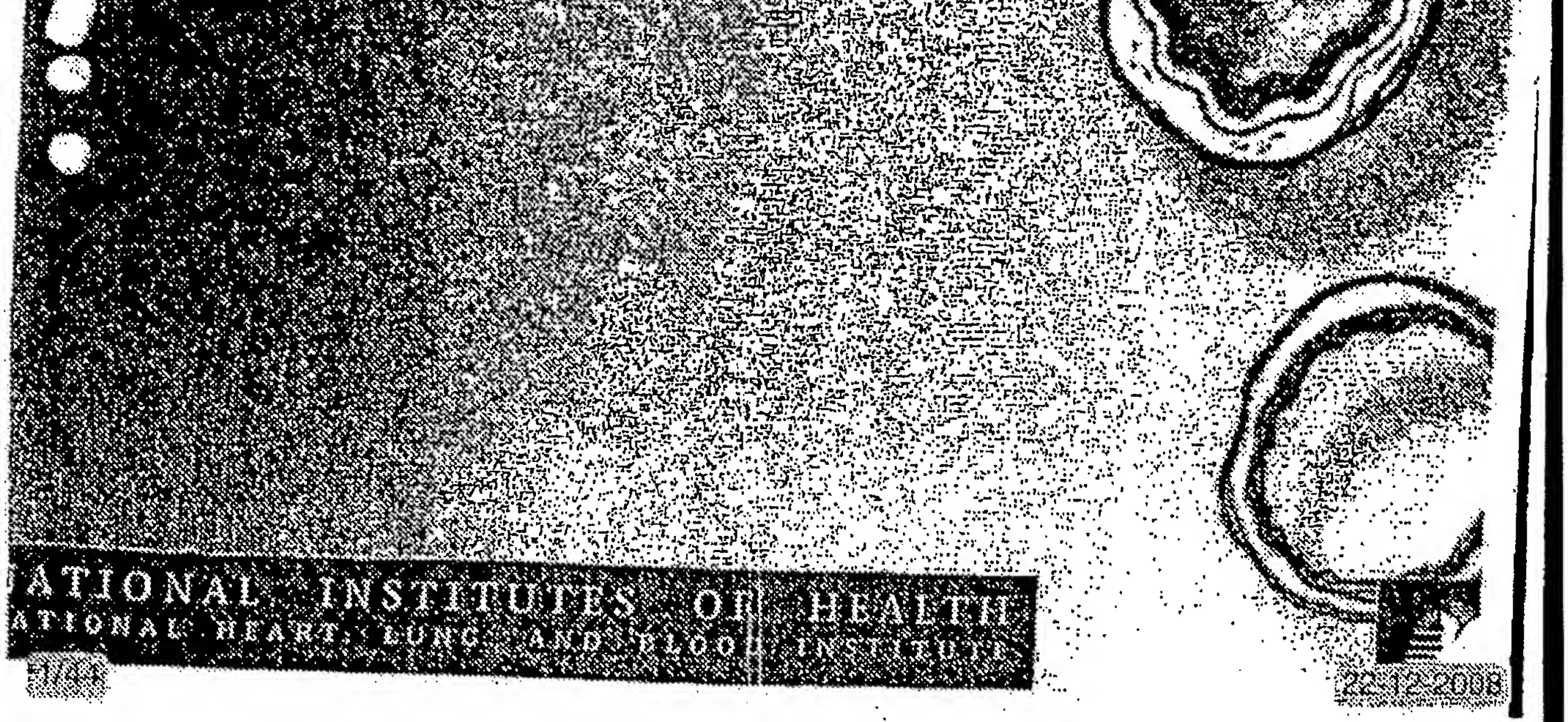
Exhibits 1-14 are listed in the Evidence Appendix attached to the Appeal Brief, and are enclosed therewith.

Exhibit 15: "Guidelines for the Diagnosis and Management of Asthma," Expert Panel Report 2, Clinical Practice Guidelines, NIH Publication No. 97-4051, July 1997, pages 57-94.

National Asthma Education and Prevention Program

EXPERT PANEL REPORT 2

Guidelines for the Diagnosis and Management of Asthma



NATIONAL INSTITUTES OF HEALTH
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

EXPERT PANEL REPORT 2

CLINICAL PRACTICE GUIDELINES

Guidelines for the Diagnosis and Management of Asthma

NIH PUBLICATION
No. 97-4051
JULY 1997

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

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COMPONENT 3: PHARMACOLOGIC THERAPY

KEY POINTS

- Underdiagnosis and inappropriate therapy are major contributors to asthma morbidity and mortality.
- Goals of asthma therapy are:
  - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
  - Maintain (near) "normal" pulmonary function
  - Maintain normal activity levels (including exercise and other physical activity)
  - Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
  - Provide optimal pharmacotherapy with minimal or no adverse effects
  - Meet patients' and families' expectations of and satisfaction with asthma care
- Persistant asthma is most effectivaly controlled with daily anti-inflammatory therapy.
- A stepwise approach to pharmacologic therapy is recommended:
  - The amount and frequency of medication is dictated by asthma severity and directed toward suppression of increasing airway inflammation.
  - Initiate therapy at a higher level at the onset to establish prompt control and then step down.
  - Continual monitoring is essential to ensure that asthma control is achieved.
  - Step down therapy cautiously once control is achieved and sustained.
  - Step-down therapy is necessary to identify the minimum medication necessary to maintain control.
- Regular followup visits (at 1- to 6-month intervals) are essential to maintain control and consider appropriate step down in therapy.
- Therapeutic strategies should be considered in concert with clinician-patient partnership strategies; education of patients is essential for achieving optimal asthma control.
- At each step, patients should be advised to avoid or control allergens, irritants, or other factors that make the patient's asthma worse.
- Referral to an asthma specialist for consultation or comanagement is recommended if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care. Referral may be considered for patients who require step 3 care. For patients younger than 3 years of age, referral is *recommended* if the patient requires step 3 or 4 care and should be *considered* if the patient requires step 2 care.
- New medications are available.
  - Long-acting inhaled $beta_2$-agonists
    - Effective 12-hour bronchodilator
    - Adjunctive therapy to inhaled corticosteroids for maintaining control, especially helpful for nighttime symptoms
    - Not to be used to treat acute symptoms or exacerbations
  - Nedocromil
    - Similar role in therapy as cromolyn sodium, with similar safety profile
  - Leukotriene modifiers
    - Zafirlukast, leukotriene receptor antagonist, and zileuton, 5-lipoxygenase inhibitor
    - May be considered alternative daily long-term-control medications for patients with mild persistent asthma who are 12 years of age and older, but further clinical experience and study are needed to establish their roles in therapy

- Increased understanding of inhaled corticosteroids notes that:
  - Inhaled corticosteroids are the most potent inhaled anti-inflammatory agent currently available.
  - Early intervention with inhaled corticosteroids can improve asthma control and normalize lung function and may prevent irreversible airway injury.
  - Higher doses of inhaled corticosteroids may be associated with possible, but not predictable, growth retardation in children. The clinical significance of this potential systemic effect has yet to be determined.
  - Issues regarding clinical comparability and bioavailability of different preparations and different delivery systems indicate the need to adjust doses accordingly.
- Management of asthma exacerbations includes:
  - Inhaled $beta_2$-agonist to provide prompt relief of airflow obstruction
  - Systemic corticosteroid, for moderate-to-severe exacerbations, to suppress and reverse airway inflammation
  - Oxygen to relieve hypoxia for moderate-to-severe exacerbations
  - Monitoring response to therapy with serial measurements of lung function

DIFFERENCES FROM 1991 EXPERT PANEL REPORT

- Medications are now categorized into two general classes: long-term-control medications used to achieve and maintain control of persistent asthma and quick-relief medications used to treat acute symptoms and exacerbations. *However, the updated report continues to emphasize that the most effective medications for long-term therapy are those shown to have anti-inflammatory effects.*
- New medications are available—long-acting inhaled $beta_2$-agonists, nedocromil, zafirlukast, and zileuton—that have positions in therapy for long-term control and prevention of symptoms.
- There is an increased understanding of inhaled corticosteroids and their significant role in asthma therapy. An estimated clinical comparability of different inhaled corticosteroid preparations is presented.
- The stepwise approach to asthma therapy emphasizes initiating higher level therapy at the onset to establish prompt control and then stepping down.
- A new section on asthma in infants and young children incorporates recent studies on wheezing in early childhood.

Selecting the appropriate pharmacologic therapy to achieve and maintain control of asthma involves several considerations: the medications and their routes of administration, a stepwise approach to managing asthma long term as a chronic disorder, and a protocol for managing exacerbations. Each will be discussed in this component. In addition, substantial reports in the literature since publication of the 1991 Expert Panel Report have commented on the safety of regular administration of inhaled $beta_2$-agonists and the potential adverse effects of inhaled corticosteroids. Because of the importance of these two classes of compounds in the treatment of asthma, it is the opinion of the Panel that special emphasis should be given to these issues. A summary is presented in this component.

The therapeutic strategies provided in this component should be considered in concert with the clinician-patient partnership strategies provided in component 4. Effective communication with, and education of, patients will increase the benefits of the therapeutic regimen.

Pharmacologic Therapy: The Medications

KEY POINTS: THE MEDICATIONS

Long-term-control medications

- Corticosteroids: Most potent and effective anti-inflammatory medication currently available. Inhaled form is used in the long-term control of asthma. Systemic corticosteroids are often used to gain prompt control of the disease when initiating long-term therapy.
- Cromolyn sodium and nedocromil: Mild-to-moderate anti-inflammatory medications. May be used as initial choice for long-term-control therapy for children. Can also be used as preventive treatment prior to exercise or unavoidable exposure to known allergens.
- Long-acting beta$_2$-agonists: Long-acting bronchodilator used concomitantly with anti-inflammatory medications for long-term control of symptoms, especially nocturnal symptoms. Also prevents exercise-induced bronchospasm (EIB).
- Methylxanthines: Sustained-release theophylline is a mild-to-moderate bronchodilator used principally as adjuvant to inhaled corticosteroids for prevention of nocturnal asthma symptoms. May have mild anti-inflammatory effect.
- Leukotriene modifiers: Zafirlukast, a leukotriene receptor antagonist, or zileuton, a 5-lipoxygenase inhibitor, may be considered an alternative therapy to low doses of inhaled corticosteroids or cromolyn or nedocromil for patients ≥12 years of age with mild persistent asthma, although further clinical experience and study are needed to establish their roles in asthma therapy.

Quick-relief medications

- Short-acting beta$_2$-agonists: Therapy of choice for relief of acute symptoms and prevention of EIB.
- Anticholinergics: Ipratropium bromide may provide some additive benefit to inhaled beta$_2$-agonists in severe exacerbations. May be an alternative bronchodilator for patients who do not tolerate inhaled beta$_2$-agonists.
- Systemic corticosteroids: Used for moderate-to-severe exacerbations to speed recovery and prevent recurrence of exacerbations.

OVERVIEW OF THE MEDICATIONS

Pharmacologic therapy is used to prevent and control asthma symptoms, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction. Recommendations in this component reflect the scientific concept that asthma is a chronic disorder with recurrent episodes of airflow limitation, mucus production, and cough. Asthma medications are thus categorized into two general classes: *long-term-control* medications taken daily on a long-term basis to achieve and maintain control of persistent asthma (these medications are also known as long-term preventive, controller, or maintenance medications) and *quick-relief* medications taken to provide prompt reversal of acute airflow obstruction and relief of accompanying bronchoconstriction (these medications are also known as reliever or acute rescue medications). Patients with persistent asthma require both classes of medication. Figures 3-1 and 3-2 present summaries of the indications, mechanisms, potential adverse effects, and therapeutic issues for currently available long-term-control and quick-relief medications.

Long-Term-Control Medications

Long-term-control medications are taken daily on a long-term basis to achieve and maintain control of persistent asthma. They include anti-inflammatory agents, long-acting bronchodilators, and leukotriene modifiers. Because eosinophilic inflammation is a constant feature of the mucosa of the airways in asthma, the most effective long-term-control medications are those that attenuate inflammation (Haahtela et al. 1991; Kerrebijn et al. 1987; van Essen-Zandvliet et al. 1992). The Expert Panel defines anti-inflammatory medications as those that cause a reduction in the markers of airway inflammation in airway tissue or airway secretions (e.g., eosinophils, mast cells, activated lymphocytes, macrophages, and cytokines; or eosinophilic cationic protein and tryptase; or extravascular leakage of albumin, fibrinogen, or other vascular protein) and thus decrease the intensity of airway hyperresponsiveness. Because many factors contribute to the inflammatory response in asthma, many

drugs may be considered anti-inflammatory. It is not yet established, however, which anti-inflammatory actions are responsible for therapeutic effects, such as reduction in symptoms, improvement in expiratory flow, reduction in airway hyperresponsiveness, prevention of exacerbations, or prevention of airway wall remodeling.

Corticosteroids

Corticosteroids are the most potent and consistently effective long-term-control medication for asthma. Their broad action on the inflammatory process may account for their efficacy as preventive therapy. Their clinical effects include reduction in severity of symptoms, improvement in peak expiratory flow and spirometry, diminished airway hyperresponsiveness, prevention of exacerbations, and possibly the prevention of airway wall remodeling (Barnes et al. 1993; Jeffery et al. 1992; Dahl et al. 1993; Fabbri et al. 1993; Gustafsson et al. 1993; Haahtela et al. 1991; Kamada et al. 1996; Rafferty et al. 1985; van Essen-Zandvliet et al. 1992). Which of these clinical effects depend on specific anti-inflammatory actions of corticosteroids is not yet clear. Corticosteroids suppress the generation of cytokines, recruitment of airway eosinophils, and release of inflammatory mediators. These anti-inflammatory actions of corticosteroids have been noted in clinical trials and analyses of airway histology (Busse 1993; Booth et al. 1995; Laitinen et al. 1992; Djukanovic et al. 1992; Duddridge et al. 1993; Laitinen et al. 1991; Levy et al. 1995; McGill et al. 1995).

Dosages for inhaled corticosteroids vary depending upon the specific product and delivery devices (see figure 3-5b). For many patients, a twice-a-day dosing schedule maintains control of asthma; even high doses of some preparations are effective when given twice a day (Noonan et al. 1995). Some studies show that once-daily dosing is effective in mild persistent asthma (Jones et al. 1994; Pincus et al. 1995).

Cromolyn Sodium and Nedocromil

Although cromolyn and nedocromil have distinct properties (Clark 1993), they have similar anti-inflammatory actions. Their mechanism appears to involve the blockade of chloride channels (Alton and Norris 1996), and they modulate mast cell mediator release and eosinophil recruitment (Eady 1986). They also inhibit the early and late asthmatic response to allergen challenge and exercise-induced bronchospasm (EIB) (Novembre et al. 1994; Alton and Norris 1996; Thompson 1989; Gonzalez and Brogden 1987).

The two compounds are equally effective against allergen challenge (Gonzalez and Brogden 1987), although nedocromil appears to be more potent than cromolyn in inhibiting bronchospasm provoked by exercise (Novembre et al. 1995; deBenedictis et al. 1995), by cold dry air (Juniper et al. 1987), and by bradykinin aerosol (Dixon and Barnes 1989).

Both compounds have been shown to reduce asthma symptoms, improve morning peak flow, and reduce need for quick-relief beta$_2$-agonists (Lai et al. 1993; Schwartz et al. 1996). Two large clinical trials comparing nedocromil MDI 4 mg qid to cromolyn MDI 2 mg qid demonstrated that they are generally comparable in mild allergic patients and that nedocromil was more effective than cromolyn in nonallergic patients using inhaled corticosteroids. Furthermore, nedocromil may have a modest effect in helping reduce the dose requirements for inhaled corticosteroids (Lai et al. 1993; O'Hickey and Rees 1994; Svendsen and Jorgensen 1991), although some studies did not demonstrate this effect (Wong et al. 1993).

Dosing recommendations for both drugs are for administration four times a day, although nedocromil has been shown to be clinically effective with twice-daily dosing (Creticos et al. 1995).

The clinical response to cromolyn and nedocromil is less predictable than the response to inhaled corticosteroids. Both compounds have a strong safety profile.

Long-Acting Beta$_2$-Agonists (Beta-Adrenergic Agonists)

The principal action of beta$_2$-agonists is to relax airway smooth muscle by stimulating beta$_2$-receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. Long-acting inhaled beta$_2$-agonists have a duration of bronchodilation of at least 12 hours after a single dose (Becker and Simons 1989; D'Alonzo et al. 1994). This class of medication is *not* to be used for exacerbations. Rather, it is used as an adjunct to anti-inflammatory therapy for providing long-term control of symptoms, especially nocturnal symptoms (Yates et al. 1995) and to prevent exercise-induced bronchospasm. The use and safety of beta$_2$-agonists are discussed on page 67, Special Issues Regarding Safety.

FIGURE 3-1. LONG-TERM-CONTROL MEDICATIONS

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Corticosteroids (Glucocorticoids) *Inhaled:* Beclomethasone dipropionate Budesonide Flunisolide Fluticasone propionate Triamcinolone acetonide	*Indications* ▪ Long-term prevention of symptoms; suppression, control, and reversal of inflammation. ▪ Reduce need for oral corticosteroid. *Mechanisms* ▪ Anti-inflammatory. Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation. ▪ Reverse beta$_2$-receptor down-regulation. Inhibit microvascular leakage.	▪ Cough, dysphonia, oral thrush (candidiasis). ▪ In high doses (see figure 3-5b), systemic effects may occur, although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis, growth suppression, and skin thinning and easy bruising) (Barnes and Pedersen 1993; Kamada et al. 1996).	▪ Spacer/holding chamber devices and mouth washing after inhalation decrease local side effects and systemic absorption. ▪ Preparations are not absolutely interchangeable on a mcg or per puff basis (see figure 3-5c for estimated clinical comparability). New delivery devices may provide greater delivery to airways, which may affect dose. ▪ The risks of uncontrolled asthma should be weighed against the limited risks of inhaled corticosteroids. The potential but small risk of adverse events is well balanced by their efficacy. (See text.) ▪ Dexamethasone is not included because it is highly absorbed and has long-term suppressive side effects.
Systemic: Methylprednisolone Prednisolone Prednisone	*Indications* ▪ For short-term (3–10 days) "burst": to gain prompt control of inadequately controlled persistent asthma. ▪ For long-term prevention of symptoms in severe persistent asthma: suppression, control, and reversal of inflammation. *Mechanisms* ▪ Same as inhaled.	▪ Short-term use: reversible, abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis of femur. ▪ Long-term use: adrenal axis suppression, growth suppression, dermal thinning, hypertension, diabetes, Cushing's syndrome, cataracts, muscle weakness, and—in rare instances—impaired immune function. ▪ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, and *Strongyloides*.	Use at lowest effective dose. For long-term use, alternate-day a.m. dosing produces least toxicity. If daily doses are required, one study shows improved efficacy with no increase in adrenal suppression when administered at 3 p.m. rather than in the morning (Beam et al. 1992).

FIGURE 3-1. LONG-TERM-CONTROL MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Cromolyn Sodium and Nedocromil	*Indications* ▪ Long-term prevention of symptoms; may modify inflammation. ▪ Preventive treatment prior to exposure to exercise or known allergen. *Mechanisms* ▪ Anti-inflammatory. Block early and late reaction to allergen. Interfere with chloride channel function. Stabilize mast cell membranes and inhibit activation and release of mediators from eosinophils and epithelial cells. ▪ Inhibit acute response to exercise, cold dry air, and SO_2.	15 to 20 percent of patients complain of an unpleasant taste from nedocromil.	▪ Therapeutic response to cromolyn and nedocromil often occurs within 2 weeks, but a 4- to 6-week trial may be needed to determine maximum benefit. ▪ Dose of cromolyn MDI (1 mg/puff) may be inadequate to affect airway hyperresponsiveness. Nebulizer delivery (20 mg/ampule) may be preferred for some patients ▪ Safety is the primary advantage of these agents.
Long-Acting Beta$_2$-Agonists *Inhaled:* Salmeterol	*Indications* ▪ Long-term prevention of symptoms, especially nocturnal symptoms, added to anti-inflammatory therapy ▪ Prevention of exercise-induced bronchospasm. ▪ *Not to be used to treat acute symptoms or exacerbations.* *Mechanisms* ▪ Bronchodilation. Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction. ▪ In vitro, inhibit mast cell mediator release, decrease vascular permeability, and increase mucociliary clearance. ▪ Compared to short-acting inhaled beta$_2$-agonist, salmeterol (but not formoterol) has slower onset of action (15 to 30 minutes) but longer duration (>12 hours).	▪ Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QT_c interval in overdose. ▪ A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established. ▪ See text for additional discussion.	▪ Not to be used to treat acute symptoms or exacerbations. ▪ Clinical significance of potentially developing tolerance is uncertain because studies show symptom control and bronchodilation are maintained. ▪ Should not be used in place of anti-inflammatory therapy. ▪ May provide more effective symptom control when added to standard doses of inhaled corticosteriod compared to increasing the corticosteriod dosage.
Oral: Albuterol, sustained-release			▪ *Inhaled long-acting beta$_2$-agonists are preferred because they are longer acting and have fewer side effects than oral sustained-release agents.*

FIGURE 3-1. LONG-TERM-CONTROL MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Methylxanthines Theophylline, sustained-release tablets and capsules	*Indications* ▪ Long-term control and prevention of symptoms, especially nocturnal symptoms. *Mechanisms* ▪ Bronchodilation. Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism ▪ May affect eosinophilic infiltration into bronchial mucosa as well as decrease T-lymphocyte numbers in epithelium. ▪ Increases diaphragm contractility and mucociliary clearance.	▪ Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia. ▪ Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males with prostatism.	▪ Maintain steady-state serum concentrations between 5 and 15 mcg/mL. Routine serum concentration monitoring is essential due to significant toxicities, narrow therapeutic range, and individual differences in metabolic clearance. Absorption and metabolism may be affected by numerous factors (see figure 3-5a), which can produce significant changes in steady-state serum theophylline concentrations. ▪ Not generally recommended for exacerbations. There is minimal evidence for added benefit to optimal doses of inhaled $beta_2$-agonists. Serum concentration monitoring is mandatory.
Leukotriene Modifiers			
Zafirlukast tablets	*Indications* ▪ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥12 years of age. *Mechanisms* ▪ Leukotriene receptor antagonist; selective competitive inhibitor of LTD4 and LTE4 receptors.	▪ No specific adverse effects to date. As with any new drug, there is possibility of rare hypersensitivity or idiosyncratic reactions that cannot usually be detected in initial premarketing trials. One reported case of reversible hepatitis and hyperbilirubinemia; high concentrations may develop in patients with liver impairment.	▪ Administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ▪ Inhibits the metabolism of warfarin and increases prothrombin time; it is a competitive inhibitor of the CYP2C9 hepatic microsomal isozymes. (It has not affected elimination of terfenadine, theophylline, or ethinyl estradiol drugs metabolized by the CYP3A4 isozymes.)
Zileuton tablets	*Indications* ▪ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥12 years of age. *Mechanisms* ▪ 5-lipoxygenase inhibitor.	▪ Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia.	▪ Zileuton is microsomal CYP3A4 enzyme inhibitor that can inhibit the metabolism of terfenadine, warfarin, and theophylline. Doses of these drugs should be monitored accordingly. ▪ Monitor hepatic enzymes (ALT).

FIGURE 3-2. QUICK-RELIEF MEDICATIONS

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Short-Acting Inhaled Beta$_2$-Agonists Albuterol Bitolterol Pirbuterol Terbutaline	*Indications* ▪ Relief of acute symptoms; quick-relief medication. ▪ Preventive treatment prior to exercise for exercise-induced bronchospasm. *Mechanisms* ▪ Bronchodilation. Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction.	Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, hyperglycemia. Inhaled route, in general, causes few systemic adverse effects. Patients with preexisting cardiovascular disease, especially the elderly, may have adverse cardiovascular reactions with inhaled therapy.	▪ Drugs of choice for acute bronchospasm. Inhaled route has faster onset, fewer adverse effects, and is more effective than systemic routes. The less beta$_2$-selective agents (isoproterenol, metaproterenol, isoetharine, and epinephrine) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses. Albuterol liquid is not recommended. ▪ For patients with mild intermittent asthma, regularly scheduled daily use neither harms nor benefits asthma control (Drazen et al. 1996). Regularly scheduled daily use is not generally recommended. ▪ Increasing use or lack of expected effect indicates inadequate asthma control. >1 canister a month (e.g., albuterol-200 puffs per canister) may indicate overreliance on this drug; ≥2 canisters in 1 month poses additional adverse risks. ▪ For patients frequently using beta$_2$-agonist, anti-inflammatory medication should be initiated or intensified.
Anticholinergics Ipratropium bromide	*Indications* ▪ Relief of acute bronchospasm (see Therapeutic Issues column). *Mechanisms* ▪ Bronchodilation. Competitive inhibition of muscarinic cholinergic receptors. ▪ Reduces intrinsic vagal tone to the airways. May block reflex bronchoconstriction secondary to irritants or to reflux esophagitis. ▪ May decrease mucus gland secretion.	Drying of mouth and respiratory secretions, increased wheezing in some individuals, blurred vision if sprayed in eyes.	▪ Reverses only cholinergically mediated bronchospasm; does not modify reaction to antigen. Does not block exercise-induced bronchospasm. ▪ May provide additive effects to beta$_2$-agonist but has slower onset of action. ▪ Is an alternative for patients with intolerance to beta$_2$-agonists. ▪ Treatment of choice for bronchospasm due to beta-blocker medication.

FIGURE 3-2. QUICK-RELIEF MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Corticosteroids *Systemic:* Methylprednisolone Prednisolone Prednisone	*Indications* ■ For moderate-to-severe exacerbations to prevent progression of exacerbation, reverse inflammation, speed recovery, and reduce rate of relapse. *Mechanisms* ■ Anti-inflammatory. See figure 3-1.	■ Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis of femur. ■ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, and *Strongyloides*.	■ Short-term therapy should continue until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3 to 10 days but may require longer. ■ There is no evidence that tapering the dose following improvement prevents relapse.

Methylxanthines

Theophylline, the principally used methylxanthine, provides mild-to-moderate bronchodilation in asthma. Although its mechanism of action has yet to be established (Weinberger and Hendeles 1996; Hendeles et al. 1995), recent evidence suggests that low serum concentrations of theophylline are mildly anti-inflammatory (Sullivan et al. 1994; Kidney et al. 1995; Pauwels 1989). Sustained-release theophylline's main use is as adjuvant therapy, and it is particularly effective for controlling nocturnal asthma symptoms. Sustained-release theophylline may be considered as an alternative, but not preferred, long-term preventive therapy when issues arise concerning cost or adherence to regimens using inhaled medication. Monitoring serum concentration levels is essential to ensure that therapeutic, but not toxic, doses are achieved.

Leukotriene Modifiers

Leukotrienes are potent biochemical mediators released from mast cells, eosinophils, and basophils that contract airway smooth muscle, increase vascular permeability, increase mucus secretions, and attract and activate inflammatory cells in the airways of patients with asthma (Henderson 1994). Two leukotriene modifiers—zafirlukast and zileuton—have recently become available as oral tablets for the treatment of asthma.

From the information currently available, it appears that leukotriene modifiers improve lung function (Gaddy et al. 1992) and diminish symptoms and the need for short-acting inhaled $beta_2$-agonists. The majority of trials have been conducted in mild-to-moderate asthma, and the improvements noted have been modest. Leukotriene modifiers may be considered an alternative to low-dose inhaled corticosteroid therapy for patients with mild persistent asthma, although increased clinical experience and further study in a wide range of patients are needed to determine those patients most likely to benefit from leukotriene modifiers and to establish a more specific role for leukotriene modifiers in asthma therapy.

Zafirlukast, a leukotriene receptor antagonist, has been demonstrated to attenuate the late response to inhaled allergen and post-allergen induced bronchial responsiveness (Dahlen et al. 1994; Taylor et al. 1991). Studies comparing zafirlukast to placebo in patients with mild-to-moderate asthma demonstrated that patients treated with zafirlukast experienced modest improvement in FEV_1 (mean improvement of 11 percent above placebo), improved symptom scores, and reduced albuterol use (average decline of 1 puff/day) (Spector et al. 1994). In a small study of healthy

males, 60 mg a day of zafirlukast caused a significant increase in the half-life of warfarin. Consequently, for those individuals receiving zafirlukast and warfarin, it will be necessary to closely monitor prothrombin times and adjust doses of warfarin accordingly.

Zileuton, a 5-lipoxygenase inhibitor, has been demonstrated to provide immediate and sustained improvements in FEV_1 (mean increase of 15 percent above placebo) in placebo-controlled trials in patients with mild-to-moderate asthma (Israel et al. 1993, 1996). Compared to placebo, the patients with moderate asthma treated with zileuton experienced significantly fewer exacerbations requiring oral corticosteroids (Israel et al. 1996), thus suggesting anti-inflammatory action. Finally, zileuton is capable of attenuating bronchoconstriction from exercise (Meltzer et al. 1996) and from aspirin in aspirin-sensitive individuals (Israel et al. 1993). Because liver toxicity has been found in some subjects receiving zileuton, it is recommended that hepatic enzymes (ALT) be monitored in patients who take this medication. Zileuton is a microsomal CYP3A4 enzyme inhibitor that can inhibit the metabolism of terfenadine, warfarin, and theophylline. Doses of these drugs should be monitored accordingly.

Quick-Relief Medications

Quick-relief medications are used to provide prompt relief of bronchoconstriction and its accompanying acute symptoms such as cough, chest tightness, and wheezing. They include short-acting $beta_2$-agonists and anticholinergics. Although the onset of action is slow (>4 hours), systemic corticosteroids are important in the treatment of moderate-to-severe exacerbations because they prevent progression of the exacerbation, speed recovery, and prevent early relapses.

Short-Acting $Beta_2$-Agonists

Short-acting $beta_2$-agonists relax airway smooth muscle and cause a prompt (within 30 minutes) increase in airflow. Inhaled short-acting $beta_2$-agonists are the drug of choice for treating acute asthma symptoms and exacerbations and for preventing EIB. Concerns about the safety of short-acting $beta_2$-agonists are discussed in another section of this component (see page 67, Special Issues Regarding Safety).

Anticholinergics

Cholinergic innervation is an important factor in the regulation of airway smooth muscle tone. Ipratropium bromide is a quaternary derivative of atropine that does not have atropine's side effects. Ipratropium bromide may provide some additive benefit with inhaled $beta_2$-agonists in severe asthma exacerbations. Its effectiveness in long-term management of asthma has not been demonstrated (Kerstjens et al. 1992; Gross 1988; Storms et al. 1986).

Systemic Corticosteroids

Systemic corticosteroids can speed resolution of airflow obstruction and reduce the rate of relapse (Fanta et al. 1983; Rowe et al. 1992; Scarfone et al. 1993; Connett et al. 1994; Chapman et al. 1991).

Medications To Reduce Oral Systemic Corticosteroid Dependence

Troleandomycin, Cyclosporine, Methotrexate, Gold, Intravenous Immunoglobulin, Dapsone, and Hydroxychloroquine

These regimens to reduce oral systemic corticosteroid dependence should be used only in selected patients who are under the supervision of an asthma specialist. Although some of the compounds have corticosteroid-sparing effects, their use in asthma remains complicated because of highly variable effects, potential toxicity, and limited clinical experience (Bernstein et al. 1996; Jarjour et al. 1996; Mullarkey et al. 1988; Shiner et al. 1990; Erzurum et al. 1991; Muranaka et al. 1978; Klaustermeyer et al. 1987; Kamada et al. 1993; Nelson et al. 1993; Alexander et al. 1992; Mazer and Gelfand 1991). Colchicine is not considered effective in reducing need for oral systemic or high doses of inhaled corticosteroids (Newman et al. 1997).

Complementary Alternative Medicine

Alternative healing methods are not substitutes for recommended pharmacologic therapy. Although alternative healing methods may be popular with selected patients and of some interest to investigators, their scientific basis has not been established.

The most widely known complementary alternative medicine methods are acupuncture, homeopathy, herbal medicine, and Ayurvedic medicine (which includes transcendental meditation, herbs, and yoga).

A review of multiple trials on the use of acupuncture in asthma concluded that the trials lacked quality and that the effectiveness of acupuncture in treating asthma has not been established (Kleijnen et al. 1991). One trial, however, demonstrated benefit in EIB (Fung et al. 1986). Homeopathy, based on the "law of similars" and the use of infinitesimally small doses, is as yet unproven for asthma (Reilly et al. 1986); some homeopathic remedies may contain potent unidentified pharmacologic agents (Morice 1986). No controlled clinical trials have been reported on herbal medicines, and the claims of effectiveness of western plant derivatives for asthma remain unsubstantiated (Dorsch and Wegner 1991; Ziment and Stein 1993). Because complementary alternative medicine is reported to be used by as much as one-third of the U.S. population (Eisenberg et al. 1993), it may be important to inquire about all the medications a patient uses and advise the patient accordingly (see component 4).

ROUTE OF ADMINISTRATION

Medications for asthma can be administered either by inhaled or systemic routes. Systemic routes are oral (ingested) or parenteral (subcutaneous, intramuscular, or intravenous). The major advantages of delivering drugs directly into the lungs via inhalation are that higher concentrations can be delivered more effectively to the airways and that systemic side effects are avoided or minimized (Newhouse and Dolovich 1986). Furthermore, the onset of action of inhaled bronchodilators is substantially shorter than that of oral bronchodilators.

Inhaled medications, or aerosols, are available in a variety of devices that differ in technique required and quantity of drug delivered to the lung. See figure 3-3 for a summary of issues to consider for different devices. Whatever device is selected, patients should be instructed in its use and their technique checked regularly.

Most inhaled medications currently used for asthma are available as metered-dose inhalers (MDIs). Historically, MDI technology has utilized chlorofluorocarbons (CFCs) as propellants. CFCs usually constitute 95 percent or more of the formulation emitted from an MDI; CFCs are metabolically stable and even the portion of an actuation that is systemically absorbed is quickly excreted unchanged via exhalation. However, CFCs have been found to deplete stratospheric ozone and have been banned internationally. Although a temporary medical exemption has been granted, it is expected that CFC-propelled MDIs will eventually be phased out completely. Alternatives include MDIs with other propellants (nonchlorinated propellants such as hydrofluoroalkane [HFA] 134a do not have ozone-depleting properties), multidose dry powder inhalers, and other hand-held devices with convenience and delivery characteristics similar to current MDIs. An MDI for albuterol with HFA 134a has been approved for use; additional non-CFC products and delivery systems are expected in the future. The Food and Drug Administration approval process requires that the replacement products demonstrate comparability to the corresponding CFC products so that clinicians and patients can anticipate similar effectiveness and safety with the new products. During the phaseout of CFC products, clinicians will need to be informed of the alternatives and assist their patients in the transition to non-CFC products (see component 4).

SPECIAL ISSUES REGARDING SAFETY

Short-Acting Inhaled Beta$_2$-Agonists

KEY POINTS: SHORT-ACTING INHALED BETA$_2$-AGONISTS

- Short-acting beta$_2$-agonists are the most effective medication for relieving acute bronchospasm.
- Increasing use of short-acting beta$_2$-agonists or the use of more than one canister in 1 month indicates inadequate control of asthma and the need for initiating or intensifying anti-inflammatory therapy.
- Regularly scheduled, daily use of short-acting beta$_2$-agonists is generally not recommended.

Short-acting inhaled beta$_2$-agonists (e.g., albuterol) are the medications of choice for treating exacerbations of asthma and for preventing EIB. Prior to 1990, many clinicians prescribed short-acting beta$_2$-agonists on a regularly scheduled basis in the belief that this treatment regimen improved overall asthma symptom control. Some recent reports, however, have modified these beliefs. For example, in *moderate* asthma, regular use of a potent inhaled beta$_2$-agonist (fenoterol) produced a significant diminution in asthma control and objective measurements of pulmonary function (Sears et al. 1990). In *mild* asthma, regularly scheduled use of albuterol compared to use on an as-needed basis only resulted in no significant differences in a variety of

FIGURE 3-3. AEROSOL DELIVERY DEVICES

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Metered-dose inhaler (MDI) Beta$_2$-agonists Corticosteroids Cromolyn sodium and nedocromil Anticholinergics	>5 years	Actuation during a slow (30 L/min or 3-5 seconds) deep inhalation, followed by 10-second breath-holding. Under laboratory conditions, open-mouth technique (holding MDI 2 inches away from open mouth) enhances delivery to the lung. However, it has not consistently been shown to enhance clinical benefit compared to closed-mouth technique (closing lips around MDI mouthpiece).	Slow inhalation may be difficult. Difficulty with coordination of actuation and inhalation, particularly in young children and elderly. Patients may incorrectly stop inhalation at actuation. Deposition of 80 percent of actuated dose in oropharynx. Mouth washing is effective in reducing systemic absorption (Selroos and Halme 1991).
Breath-actuated MDI Beta$_2$-agonists	>5 years	Slow (30 L/min or 3-5 seconds) inhalation followed by 10-second breath-holding.	Indicated for patients unable to coordinate inhalation and actuation. May be particularly useful in elderly (Newman et al. 1991). Slow inhalation may be difficult and patients may incorrectly stop inhalation at actuation. Requires more rapid inspiration to activate than is optimal for deposition. Cannot be used with currently available spacer/holding chamber devices.
Dry powder inhaler (DPI) Beta$_2$-agonists Corticosteroids		Rapid (60 L/min or 1-2 seconds), deep inhalation. Minimally effective inspiratory flow is device dependent.	Dose lost if patient exhales through device. Delivery may be >MDI depending on device and technique. Can be used in children 4 years old, but effects are more consistent with children >5 (Pedersen et al. 1990; Goren et al. 1994; Kemp et al. 1989; Kasten et al. 1994). Most appear to have similar delivery efficiency as MDI either with or without spacer/holding chamber, but some may have delivery >MDI (Thorsson et al. 1994; Agertoft and Pedersen 1993; Kemp et al. 1989; Melchor et al. 1993; Vidgren et al. 1983). Mouth washing is effective in reducing systemic absorption (Selroos and Halme 1991).

FIGURE 3-3. AEROSOL DELIVERY DEVICES (CONTINUED)

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Spacer/holding chamber	>4 years <4 years with face mask	Slow (30 L/min or 3-5 seconds) inhalation or tidal breathing immediately following actuation. Actuation only once into spacer/holding chamber per inhalation (O'Callaghan et al. 1994). If face mask is used, allow 3-5 inhalations per actuation (Everard et al. 1992).	Easier to use than MDI alone. With a face mask, enables MDI to be used with small children (Everard et al. 1992; Connett et al. 1993). Simple tubes do not obviate coordinating actuation and inhalation. Bulky. Output may be reduced in some devices after cleaning. The larger volume spacers/holding chambers (>600 cc) may increase lung delivery over MDI alone in patients with poor MDI technique. The effect of a spacer/holding chamber on output from an MDI is dependent on both MDI and spacer type; thus data from one combination should not be extrapolated to all others (Ahrens et al. 1995; Kim et al. 1987). Spacers/holding chambers decrease oropharyngeal deposition and will reduce potential system absorption of inhaled corticosteroid preparations that have higher oral bioavailability (Newman et al. 1984; Brown et al. 1990; Lipworth 1995; Setroos and Haime 1991). Spacers/holding chambers are recommended for all patients on medium-to-high doses of inhaled corticosteroids. May be as effective as nebulizer in delivering high doses of beta$_2$-agonists during severe exacerbations.
Nebulizer Beta$_2$-agonists Cromolyn Anticholinergics Corticosteroids	≤2 years Patients of any age who cannot use MDI with spacer/holding chamber or spacer and face mask (e.g., during exacerbations)	Slow tidal breathing with occasional deep breaths. Tightly fitting face mask for those unable to use mouthpiece.	Less dependent on patient coordination or cooperation. Delivery method of choice for cromolyn in children and for high-dose beta$_2$-agonists and anticholinergics in moderate-to-severe exacerbations in all patients. Expensive; time consuming; bulky; output is device dependent; and there are significant internebulizer and intranebulizer output variances.

* See figure 4-3 for description of MDI and DPI techniques.

Sources: Agertoft and Pedersen 1993; Ahrens et al. 1995; Brown et al. 1990; Connett et al. 1993; Higgins et al. 1987; Crompton and Duncan 1989; Everard et al. 1992; Fuglsang and Pedersen 1986; Goren et al. 1994; Kemp et al. 1989; Kesten et al. 1994; Kim et al. 1987; Lipworth 1995; Melchor et al. 1993; Newman et al. 1981, 1984, 1991; O'Callaghan et al. 1994; Pedersen et al. 1990; Pedersen and Mortensen 1990; Prahl and Janson 1987; Rossing et al. 1980; Ruggins et al. 1993; Schecker et al. 1993; Setroos and Haime 1991; Setroos et al. 1995; Thorsson et al. 1994; Vidgren et al. 1983.

outcome indices. Although regularly scheduled use of beta$_2$-agonists in mild asthma produced no harmful effects in a 4-month period, it also produced no demonstrable benefits (Drazen et al. 1996). Similar findings were noted in studies with moderate asthma (D'Alonzo et al. 1994; Pearlman et al. 1992). Based on these and other observations (Cockcroft et al. 1993; van Schayck et al. 1991; O'Connor et al. 1992; Mullen et al. 1993; Ernst et al. 1993; Sulssa et al. 1994), the regularly scheduled, daily use of short-acting beta$_2$-agonists is not generally recommended.

The frequency of beta$_2$-agonist use can be clinically useful as a barometer of disease activity because increasing use of beta$_2$-agonists has been associated with increased risk for death or near death in patients with asthma (Spitzer et al. 1992). The use of more than one beta$_2$-agonist canister (e.g., albuterol, 200 puffs per canister) predominantly for quick-relief treatment during a 1-month period most likely indicates overreliance on this drug and suggests inadequate asthma control (Spitzer et al. 1992).

Long-Acting Inhaled Beta$_2$-Agonists

KEY POINTS: LONG-ACTING INHALED BETA$_2$-AGONISTS

- Long-acting beta$_2$-agonists (salmeterol) can be beneficial to patients when added to inhaled corticosteroid therapy, especially to control nighttime symptoms (Greening et al. 1994; Woolcock et al. 1996). Daily use of long-acting beta$_2$-agonists should generally not exceed 84 mcg (salmeterol; four puffs).
- *Salmeterol is not to be used for treatment of acute symptoms or exacerbations.*
- Patient education regarding correct use of salmeterol is critical.
- Patients should be instructed not to stop anti-inflammatory therapy while taking salmeterol even though their symptoms may significantly improve.

Long-acting beta$_2$-agonists have several beneficial clinical properties. They attenuate EIB for longer time periods than do short-acting beta$_2$-agonists (Green and Price 1992; Henriksen et al. 1992) and improve nocturnal asthma symptoms (Fitzpatrick et al. 1990; Maesen et al. 1990). Recent studies suggest that for patients with inadequate symptom control who are receiving low-to-medium doses of inhaled corticosteroids, it may be more beneficial to add salmeterol than to increase the dose of inhaled corticosteroids (Greening et al. 1994; Woolcock et al. 1996). Furthermore, in one study, salmeterol resulted in statistically significant increases in overall quality of life (Juniper et al. 1995) although the clinical significance of the reported differences is not certain.

Several studies report that patients do not appear to develop a tolerance to the bronchodilator action of salmeterol even after months of regular treatment (D'Alonzo et al. 1994; Lotvall et al. 1992; Pearlman et al. 1992; Ullman et al. 1990). In contrast, in bronchoprovocation studies following chronic administration of either short-acting or long-acting beta$_2$-agonists, a decrease was demonstrated in the bronchoprotective effect against exercise (Ramage et al. 1994), allergen (Cockcroft et al. 1993, 1995; Bhagat et al. 1996), and methacholine (Bhagat et al. 1996; Cheung et al. 1992). However, the bronchoprotective effect over time, although diminished, was still significantly greater than placebo. Thus, the clinical importance of the reported decrease in bronchoprotective effect remains uncertain (McFadden 1995).

Following the introduction of salmeterol into clinical practice, case reports of sudden severe attacks of asthma (Clark et al. 1993) raised concerns that in certain asthma patients, under certain conditions, the use of salmeterol may cause a sudden worsening of symptoms and possibly death. A recent randomized study in England compared more than 16,000 patients who received regular salmeterol for a 16-week period with more than 8,000 patients receiving regular (qid) albuterol therapy. The study found more deaths in the salmeterol group; however, the differences did not reach statistical significance (Castle et al. 1993). Nor did a prescription-event monitoring survey demonstrate a statistically significant difference in deaths (Mann et al. 1996). Several large studies have demonstrated that, overall, patients taking salmeterol do not experience an increase in the frequency of exacerbations (Britton et al. 1992; Lundback et al. 1993; Greening et al. 1994; Pearlman et al. 1992; Woolcock et al. 1996). There are ongoing longitudinal studies to determine if there might be risk for special populations. The potential for patients to incorrectly use salmeterol as a quick-relief medication warrants special attention by the clinician and appropriate patient education. Based on current information, long-acting inhaled beta$_2$-agonists should be used only in conjunction with anti-inflammatory medication. When added to inhaled corticosteroids, long-acting inhaled beta$_2$-agonists are helpful long-term-control therapy.

Inhaled Corticosteroids

KEY POINTS: INHALED CORTICOSTEROIDS

- Inhaled corticosteroids are the most effective long-term therapy available for mild, moderate, or severe persistent asthma; in general, inhaled corticosteroids are well tolerated and safe at the recommended dosages.
- The potential but small risk of adverse events from the use of inhaled corticosteroids is well balanced by their efficacy.
- To reduce the potential for adverse effects, the following measures are recommended:
  - —Administer inhaled corticosteroids with spacers/holding chambers.
  - —Advise patients to rinse their mouths (rinse and spit) following inhalation.
  - —Use the lowest possible dose of inhaled corticosteroid to maintain control.
  - —To maintain control of asthma (especially for nocturnal symptoms), consider adding a long-acting inhaled $beta_2$-agonist to a low-to-medium dose of inhaled corticosteroid rather than using a higher dose of inhaled corticosteroid.
  - —For children, monitor growth (see box on page 72).
  - —For postmenopausal women, consider supplements of calcium (1,000 to 1,500 mg per day) and vitamin D (400 units a day). Estrogen replacement therapy, where appropriate, may be considered for patients on doses that exceed 1,000 mcg of inhaled corticosteroid a day.

Inhaled corticosteroids are the most effective long-term therapy available for patients with persistent asthma. In general, inhaled corticosteroids are well tolerated and safe at the recommended dosages (Barnes 1995; van Essen-Zandvliet et al. 1992; Tinkelman et al. 1993). Systemic effects have been identified, particularly at high doses (see figure 3-5b for a definition of high-, medium-, and low-dose inhaled corticosteroids), but their clinical significance remains unclear. Furthermore, there may be interindividual variations in dose-response effects, and thus some patients may experience effects at lower doses. (See Key Points above for a summary of recommendations to minimize the potential for adverse effects.) In general, the potential for adverse effects must be weighed against the risk of uncontrolled asthma; to date evidence supports the use of inhaled corticosteroids, especially at low and medium doses.

Local Adverse Effects

Oral candidiasis (thrush) is one of the most common adverse effects of inhaled corticosteroids. Positive throat cultures of *Candida* can be identified in about 45 to 58 percent of patients, whereas clinical thrush is diagnosed in only 0 to 34 percent of patients (Rinehart et al. 1975; Toogood et al. 1980; Shaw and Edmunds 1986). With lower dosages of inhaled corticosteroids, candidiasis is uncommon (5 percent) (Rinehart et al. 1975), although it is more frequent in adults than in children. Prevention and treatment: Use a spacer/holding chamber to reduce the incidence of colonization and clinical thrush, rinse mouth with water after inhalation (Selroos and Haime 1991), and administer inhaled corticosteroids less frequently (bid vs. qid). Topical or oral antifungal agents should be used to treat active infections.

Dysphonia is reported in 5 to 50 percent of patients using inhaled corticosteroids and is associated with vocal stress and increasing dosages of inhaled corticosteroids (Toogood et al. 1980). Prevention and treatment: Use a spacer/holding chamber, temporarily reduce dosage, or rest for vocal stress.

Reflex cough and bronchospasm can be reduced by slower rates of inspiration and/or use of a spacer/holding chamber or pretreatment with an inhaled $beta_2$-agonist. There is no convincing evidence that the routine use of an inhaled $beta_2$-agonist prior to each dose of inhaled corticosteroids increases intrapulmonary delivery of the inhaled corticosteroid or reduces dosage requirement.

Systemic Adverse Effects

Linear Growth. The potential effects of inhaled corticosteroids on children's growth are important because the drugs are more likely to be used for longer periods of time, although it is recognized that poorly controlled asthma itself may result in retarded linear growth. Growth in children with asthma who have not received any form of corticosteroid therapy may be influenced by concomitant atopy, asthma severity, and being male, among other factors (Kamada and Szefler 1995; Allen 1996). Indeed, childhood asthma appears to be associated with

KEY POINTS: INHALED CORTICOSTEROIDS AND LINEAR GROWTH IN CHILDREN

- The potential risks of inhaled corticosteroids are well balanced by their benefits.
- Growth rates are highly variable in children. Short-term evaluations may not be predictive of attaining final adult height.
- Poorly controlled asthma may delay growth in children.
- In general, children with asthma tend to have longer periods of reduced growth rates prior to puberty (males > females).
- The potential for adverse effects on linear growth from inhaled corticosteroids appears to be dose dependent. In treating children with *mild-to-moderate persistent asthma*, medium-dose inhaled corticosteroid therapy may be associated with a possible, but not predictable, adverse effect on linear growth. The clinical significance of this potential systemic effect has yet to be determined. High doses of inhaled corticosteroids have greater potential for growth suppression.
- Use of high doses of inhaled corticosteroids with children with *severe persistent asthma* has significantly less potential for having an adverse effect on linear growth than oral systemic corticosteroids.
- A majority of studies of the use of inhaled corticosteroids by children have not demonstrated an effect on growth, but a few have identified growth delay. Some caution (e.g., monitoring growth, stepping down therapy when possible) is suggested while this issue is studied further.

delayed maturation and a longer period of reduced growth prior to puberty. Although this could be viewed as growth suppression, these delays do not appear to compromise the attainment of final predicted adult heights (Balfour-Lynn 1986; Allan 1996).

Because of these numerous confounding factors, evaluating the effects of systemic or inhaled corticosteroids on growth in children with asthma has been challenging and has led to contradictory findings.

A few studies of children with asthma have identified some growth delay in those treated with inhaled corticosteroids, suggesting that some caution may be prudent until this important issue can be studied further. A 1-year controlled trial comparing children with mild-to-moderate asthma receiving either inhaled beclomethasone (400 mcg per day, administered without a spacer/holding chamber) or oral theophylline demonstrated slower growth in children receiving beclomethasone (Tinkelman et al. 1993). In a placebo-controlled, community-based 7-month study of 7- to 9-year-old children to determine the effect on growth during treatment with beclomethasone at 400 mcg/day, growth was significantly decreased in both males and females, and there was no evidence of catchup growth during a 5-month washout period (Doull et al. 1995). However, the results of this short-term study may not reflect effects on long-term growth.

A recent meta-analysis of the influence of inhaled beclomethasone in the attainment of expected adult height did not find any significant adverse effects regardless of dose, duration of asthma, or disease severity (Allen et al. 1994). An uncontrolled followup study (mean duration of 2.7 years, range of 1 to 5 years) of prepubertal children with moderate asthma found no effect of inhaled budesonide (800 mcg mean daily dose) on long-term growth (Ninan and Russell 1992). A majority of studies do not demonstrate a negative effect on growth with dosages of 400 to 800 mcg a day (Wolthers 1996; Kamada et al. 1996; Kamada and Szefler 1995; Barnes and Pederson 1993).

Bone Metabolism/Osteoporosis. The few published observations regarding the effect of inhaled corticosteroids on bone metabolism and osteoporosis are complicated by oral corticosteroid use and small patient populations (Jennings et al. 1991a, 1991b; Toogood et al. 1991). The effects of inhaled corticosteroid on markers of skeletal metabolism—serum osteocalcin, serum alkaline phosphatase, and urinary hydroxyproline:creatinine ratio—are equivocal (Hodsman et al. 1991; Jennings et al. 1991a; Ali et al. 1991). The clinical implications in terms of risk of osteoporosis and fracture after long-term use of inhaled corticosteroids are still unknown (Jennings et al. 1991b; Pouw et al. 1991). Although low and medium dosages of inhaled corticosteroids appear to have no major adverse effects on any clinically important measure of bone metabolism (Toogood et al. 1991, 1995), a dose-dependent, yet significant, reduction in bone mineral content of subjects with asthma has been associated with inhaled corticosteroid use (Packe et al. 1992; Puolijoki et al. 1992; Toogood

et al. 1988). Elderly female patients may be more at risk due to preexisting osteoporosis, previous use of oral corticosteroids, a sedentary lifestyle, and the normal changes of estrogen in aging that affect calcium utilization. However, the risk of uncontrolled asthma, which may unnecessarily limit the patient's mobility and activities, must be weighed against the limited risks of using inhaled corticosteroids. Prevention and treatment: Concurrent treatment with calcium supplements and vitamin D (and estrogen replacement where appropriate) is reasonable.

Disseminated Varicella. Although high doses of inhaled corticosteroids theoretically present risks similar to those of systemic corticosteroids, the reports of disseminated varicella in patients receiving only inhaled corticosteroids are rare, causality is not clear, and there is no evidence that recommended doses of inhaled corticosteroids are immunosuppressive. Cases have been reported of children with severe persistent asthma on immunosuppressive doses of systemic corticosteroids developing fatal disseminated disease from varicella infection (Kasper and Howe 1990; Silk et al. 1988). Other case reports indicate complications for patients with *Strongyloides* or tuberculosis who take high doses of systemic corticosteroids. Prevention and treatment: Children who require episodic therapy with systemic corticosteroids who have not had clinical varicella should receive the varicella vaccine. The vaccine should not be administered to patients who are receiving immunosuppressive doses of systemic corticosteroids (2 mg/kg or more of prednisone equivalent or 20 mg/day of prednisone for more than 1 month), unless this dosage is discontinued for at least 1 month. Children who have completed a short prednisone course may receive varicella vaccine without delay (American Academy of Pediatrics 1995; CDC 1994). Children and adults on treatment with immunosuppressive doses of corticosteroids who have not been immunized against varicella and are exposed to varicella infection are candidates for zoster immunoglobulin and therapy with oral acyclovir. Should they develop clinical varicella, intravenous acyclovir with or without zoster immunoglobulin should be given.

Dermal thinning and increased ease of skin bruising have been observed in elderly subjects treated with inhaled corticosteroids. The effect is dose dependent, but the threshold dose is variable (Capewell et al. 1990).

Hypothalamic Pituitary Axis (HPA) Function. The issue of inhaled corticosteroid effects on HPA function is complex and requires further study. Several studies indicate that low-to-medium doses of inhaled corticosteroids do not appear to have significant effects on HPA function (Doull et al. 1995; Goldstein and Konig 1983). However, some studies showed that, compared with placebo, both beclomethasone and budesonide reduced the 24-hour urinary cortisol excretion even in doses as low as 400 to 500 mcg daily (Tabachnik and Zadik 1991; Prahl 1991). At higher doses, there appears to be a dose-dependent effect on different measures of HPA function (Kamada et al. 1996; Brown et al. 1993). Fluticasone caused greater adrenal suppression at doses of 400 to 2,000 mcg than budesonide in equivalent doses (Clark et al. 1996; Boorsma et al. 1996). The clinical significance, if any, of these findings is not known.

Cataracts. Although cataracts are a documented adverse effect of systemic corticosteroids, there appears to be no association between inhaled corticosteroids and posterior subcapsular cataracts in adults (Toogood et al. 1993) or children (Simons et al. 1993; Rooklin et al. 1979).

Glucose Metabolism. In a study of children, inhaled corticosteroids at dosages from 400 to 1,000 mcg/day (budesonide) failed to affect fasting glucose or glycated hemoglobin (Turpeinen et al. 1991). At 1,000 mcg/day, a significantly greater rise in fasting serum insulin levels and glucose during a glucose tolerance test was noted, but results remained within normal limits.

REFERENCES

Agertoft L, Pedersen S. Importance of the inhalation device on the effect of budesonide. *Arch Dis Child* 1993;69:130-3.

Ahrens R, Lux C, Bahl T, Han SH. Choosing the metered-dose inhaler spacer or holding chamber that matches the patient's need: evidence that the specific drug being delivered is an important consideration. *J Allergy Clin Immunol* 1995;96:288-94.

Alexander AG, Barnes NC, Kay AB. Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. *Lancet* 1992;339:324-8.

Ali NJ, Capewell J, Ward MJ. Bone turnover during high dose inhaled corticosteroid treatment. *Thorax* 1991;46:160-4.

Allen DB. Growth suppression by glucocorticoid therapy. In: Vassalio J, ed. *Endocrinology and Metabolism Clinics in North America*. Philadelphia: W.B. Saunders Co. 1996;699-717.

Allen DB, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol* 1994;93:967-76.

Alton E, Norris AA. Chloride transport and the actions of nedocromil sodium and cromolyn sodium in asthma. *J Allergy Clin Immunol* 1996;98:S102-6.

American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for the use of live attenuated varicella vaccine. *Pediatrics* 1995;5:791-6.

Balfour-Lynn L. Growth and childhood asthma. *Arch Dis Child* 1986;61(11):1049-55.

Barnes NC, Marone G, Di Maria GU, Visser S, Utema I, Payne SL. A comparison of fluticasone propionate, 1 mg daily with beclomethasone dipropionate, 2 mg daily, in the treatment of severe asthma. *Eur Respir J* 1993;6:877-85.

Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis* 1993;148:S1-S26.

Beam WR, Weiner DE, Martin RJ. Timing of prednisone and alterations of airways inflammation in nocturnal asthma. *Am Rev Respir Dis* 1992;146(6):1524-30.

Becker AB, Simons FE. Formoterol, a new long-acting selective beta$_2$-adrenergic receptor agonist: double-blind comparison with salbutamol and placebo in children with asthma. *J Allergy Clin Immunol* 1989;84:891-5.

Bernstein IL, Bernstein DI, Dubb JW, Fairfirman I, Wallin B, and participants of the Auranofin Multicentar Drug Trial. A placebo-controlled multicentar study of auranofin in the treatment of patients with corticosteroid-dependent asthma. *J Allergy Clin Immunol* 1996;98:317-24.

Bhagat R, Swystun VA, Cockcroft DW. Salbutamol-induced increased airway responsiveness to allergen and reduced protection versus methacholine dose response. *J Allergy Clin Immunol* 1996;97:47-52.

Boorsma M, Andersson N, Larsson P, Ullman A. Assessment of the relative systemic potency of inhaled fluticasone and budesonide. *Eur Respir J* 1996;9:1427-32.

Booth H, Richmond I, Ward C, Gardiner PV, Harkawat R, Walters EH. Effect of high dose inhaled fluticasone propionate on airway inflammation in asthma. *Am J Respir Crit Care Med* 1995;152:45-52.

Britton MG, Earnshaw JS, Palmer JBD. A twelve month comparison of salmeterol with salbutamol in asthmatic patients. *Eur Respir J* 1992;5:1062-7.

Brown PH, Matuslewicz SP, Shearing C, Tibi L, Greening AP, Crompton GK. Systemic effects of high dose inhaled steroids: comparison of beclomethasone dipropionate and budesonide in healthy subjects. *Thorax* 1993;48:967-73.

Brown PH, Blundell G, Greening AP, Crompton GK. Do large volume spacer devices reduce the systemic effects of high dose inhaled corticosteroids? *Thorax* 1990;45:736-9.

Busse WW. What role for inhaled steroids in chronic asthma? *Chest* 1993;104:1565-71.

Capewell S, Reynolds S, Shuttleworth D, Edwards C, Finlay AY. Purpura and dermal thinning associated with high dose inhaled corticosteroids. *BMJ* 1990;300:1548-51.

Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306:1034- 7.

Centers for Disease Control and Prevention. General recommendations on immunization. *Morb Mortal Wkly Rep* 1994;Jan 28;43(RR-1):1-38.

Chapman KR, Verbeek PR, White JG, Rebuck AS. Effect of a short course of prednisone in the prevention of early relapse after the emergency room treatment of acute asthma. *N Engl J Med* 1991;324:788-94.

Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. Long-term effects of a long-acting beta$_2$-adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992;327:1198-203.

Clark B. General pharmacology, pharmacokinetics, and toxicology of nedocromil sodium. *J Allergy Clin Immunol* 1993;92:200-2.

Clark CE, Ferguson AD, Siddorn JA. Respiratory arrests in young asthmatics on salmeterol. *Respir Med* 1993;87(3):227-8.

Clark DJ, Grove A, Cargill RI, Lipworth BJ. Comparative adrenal suppression with inhaled budesonide and fluticasone propionate in adult asthmatic patients. *Thorax* 1996;51:262-6.

Cockcroft DW, McParland CP, Britto SA, Swystun Va, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993;342:833-7.

Cockroft DW, O'Byrne PM, Swystun VA, Bhagat R. Regular use of inhaled albuterol and the allergen-induced late asthmatic response. *J Allergy Clin Immunol* 1995;96:44-9.

Connett GJ, Warde C, Wooler E, Lenney W. Use of budesonide in severe asthmatics aged 1-3 years. *Arch Dis Child* 1993;69:351-5.

Connett GJ, Warde C, Wooler E, Lenney W. Prednisolone and salbutamol in the hospital treatment of acute asthma. *Arch Dis Child* 1994;70:170-3.

Creticos P, Burk J, Smith L, Comp R, Norman P, Findlay S. The use of twice daily nedocromil sodium in the treatment of asthma. *J Allergy Clin Immunol* 1995;95:829-36.

Crompton G, Duncan J. Clinical assessment of a new breath-actuated inhaler. *Practitioner* 1989;233:268-9.

D'Alonzo GE, Nathan RA, Henochowicz S, Morris RJ, Ratner P, Rennard SI. Salmeterol xinafoate as maintenance therapy compared with albuterol in patients with asthma. *JAMA* 1994;271:1412-6.

Dahl R, Lundback E, Malo JL, et al. A dose-ranging study of fluticasone propionate in adult patients with moderate asthma. *Chest* 1993;104:1352-8.

Dahlen B, Zetterstrom O, Bjorck T, Dahlen SE. The leukotriene-antagonist IC:204, 219 inhibits the early airway reaction to cumulative bronchial challenge with allergen in atopic asthmatics. *Eur Respir J* 1994;7:324-31.

de Benedictis FM, Tutari G, Pazzelli P, Bertotto A, Bruni L, Vaccaro R. Cromolyn versus nedocromil: duration of action in exercise-induced asthma in children. *J Allergy Clin Immunol* 1995;96:510-4.

Dixon CMS, Barnes PJ. Bradykinin-induced bronchoconstriction: inhibition by nedocromil sodium and sodium cromoglycate. *Br J Clin Pharmacol* 1989;27:831-6.

Djukanovic R, Wilson TW, Britten KM, et al. Effect of an inhaled corticosteroid on airway inflammation and symptoms of asthma. *Am Rev Respir Dis* 1992;145:669-74.

Dorsch W, Wagner H. New antiasthmatic drugs from traditional medicine? *Int Arch Allergy Anat Immunol* 1991;94:262-5.

Doull IJM, Freezer NJ, Holgate ST. Growth of pre-pubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;151:1715-9.

Drazen JM, Israel E, Boushey HA, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. *N Engl J Med* 1996;335:841-7.

Duddridge M, Ward C, Hendrick DJ, Walters EH. Changes in bronchoalveolar lavage inflammatory cells in asthmatic patients with high dose inhaled beclomethasone dipropionate. *Eur Respir J* 1993;6:487-97.

Eady RP. The pharmacology of nedocromil sodium. *Eur J Respir Dis* 1986;147(Suppl):112-9.

Eisenberg DM, Kessler REC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *N Engl J Med* 1993;328:246-52.

Ernst P, Habbick B, Suissa S, et al. Is the association between inhaled beta-agonist use and life-threatening asthma because of confounding by severity? *Am Rev Respir Dis* 1993;148:75-9.

Erzurum SC, Lett JA, Cochran JE, et al. Lack of benefit of methotrexate in severe, steroid-dependent asthma. *Ann Intern Med* 1991;114:353-60.

Everard ML, Clark AR, Milner AD. Drug delivery from holding chambers with attached facemask. *Arch Dis Child* 1992;67:580-5.

Fabbri L, Burge PS, Croonenborgh L, et al. on behalf of an International Study Group. Comparison of fluticasone propionate with beclomethasone dipropionate in moderate to severe asthma treated for one year. *Thorax* 1993;48:817-23.

Fanta CH, Rossing TH, McFadden ER Jr. Glucocorticoids in acute asthma. A critical controlled trial. *Am J Med* 1983;74:845-51.

Fitzpatrick MF, Mackay T, Driver H, Douglas NJ. Salmeterol in nocturnal asthma: a double blind, placebo controlled trial of a long acting inhaled $beta_2$-agonist. *BMJ* 1990;301:1365-8.

Fuglsang G, Pedersen S. Comparison of Nebunaler and nebulizer treatment of acute severe asthma in children. *Eur J Respir Dis* 1986;69:109-13.

Fung KP, Chow OK, So SY. Attenuation of exercise-induced asthma by acupuncture. *Lancet* 1986;2:1419-22.

Gaddy JN, Margolskee DJ, Bush RK, Williams VC, Busse WW. Bronchodilation with a potent and selective leukotriene D4 (LTD4) receptor antagonist (MK-571) in patients with asthma. *Am Rev Respir Dis* 1992;146(2):358-63.

Goldstein DE, Konig P. Effect of inhaled beclomethasone dipropionate on hypothalamic-pituitary-adrenal axis function in children with asthma. *Pediatrics* 1983;72:60-4.

Gonzalez JP, Brogden RN. Nedocromil sodium. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of reversible obstructive airways disease. *Drugs* 1987;34:550-77.

Goren A, Noviski N, Avital A, et al. Assessment of the ability of young children to use a powder inhaler device (Turbuhaler). *Pediatr Pulmonol* 1994;18:77-80.

Green CP, Price JF. Prevention of exercise induced asthma by inhaled salmeterol xinafoate. *Arch Dis Child* 1992;67:1014-7.

Greening AP, Wind P, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994;344:219-24.

Gross NJ. Ipratropium bromide. *N Engl J Med* 1988;319:486-94.

Gustafsson P, Tsanakas J, Gold M, Primhak R, Radford M, Gilles E. Comparison of the efficacy and safety of inhaled fluticasone 200 mcg/day with inhaled beclomethasone dipropionate 400 mcg/day in mild and moderate asthma. *Arch Dis Child* 1993;69:206-11.

Haahtela T, Jarvinen M, Kava T, et al. Comparison of a $beta_2$-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.

Hendeles L, Harman E, Huang D, O'Brien R, Blake K, Delafuente J. Theophylline attenuation of airway responses to allergen: comparison with cromolyn metered-dose inhaler. *J Allergy Clin Immunol* 1995;95:505-14.

Henderson WR Jr. The role of leukotrienes in inflammation. *Ann Intern Med* 1994;121:684-97.

Henriksen JM, Agertoft L, Pedersen S. Protective effect and duration of action of inhaled formoterol and salbutamol on exercise-induced asthma in children. *J Allergy Clin Immunol* 1992;89:1176-82.

Higgins RM, Cookson W, Lane DJ, John SM, McCarthy GL, McCarthy ST. Cardiac arrythmias caused by nebulized beta-agonist therapy. *Lancet* 1987;2:863-4.

Hodsman AB, Toogood JH, Jennings B, Fraher LJ, Baskerville JC. Differential effects of inhaled budesonide and oral prednisolone on serum osteocalcin. *J Clin Endocrinol Metab* 1991;72:530-40.

Israel E, Fischer AR, Rosenberg MA, et al. The pivotal role of 5-lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin. *Am Rev Respir Dis* 1993;148:1447-51.

Israel E, Cohn J, Dube L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. *JAMA* 1996;275:931-6.

Jarjour N, Gelfand E, McGill K, Busse WW. Alternative anti-inflammatory and immunomodulatory therapy. In: Szefler J, Leung DYM, eds. *Severe Asthma. Pathogenesis and Clinical Management*. New York: Marcel Dekker, 1996, pp. 333-69.

Jeffery PK, Godfrey RW, Adelroth E, Nelson F, Rogers A, Johansson SA. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. *Am Rev Respir Dis* 1992;145:890-9.

Jennings BH, Andersson KE, Johansson SA. The assessment of the systemic effects of inhaled glucocorticosteroids. The effects of inhaled budesonide vs oral prednisolone on calcium metabolism. *Eur J Clin Pharmacol* 1991a;41:11-6.

Jennings BH, Andersson KE, Johansson SA. Assessment of systemic effects of inhaled glucocorticosteroids: comparison of the effects of inhaled budesonide and oral prednisolone on adrenal function and markers of bone turnover. *Eur J Clin Pharmacol* 1991b;40:77-82.

Jones AH, Langdon CG, Lee PS, et al. Pulmicort Turbuhaler once daily as initial prophylactic therapy for asthma. *Respir Med* 1994;88:293-9.

Juniper EF, Kline PA, Morris MM, Hargreave FE. Airway constriction by isocapnic hyperventilation of cold, dry air: comparison of magnitude and duration of protection by nedocromil sodium and sodium cromoglycate. *Clin Allergy* 1987;17:523-8.

Juniper EF, Johnston PR, Borkhoff CM, Guyatt GH, Boulet LP, Haukioja A. Quality of life in asthma clinical trials: comparison of salmeterol and salbutamol. *Am J Respir Crit Care Med* 1995;151:66-70.

Kamada AK, Hill MR, Ikle DN, Bremner AM, Szefler SJ. Efficacy and safety of low-dose troleandomycin therapy in children with severe, steroid-requiring asthma. *J Allergy Clin Immunol* 1993;91:873-82.

Kamada AK, Szefler SJ. Glucocorticoids and growth in asthmatic children. *Pediatr Allergy Immunol* 1995;6:145-54.

Kamada AK, Szefler SJ, Martin RJ, et al. and the Athma Clinical Research Network. Issues in the use of inhaled glucocorticoids. *Am J Respir Crit Care Med* 1996;153:1739-48.

Kasper WJ, Howe PM. Fatal varicella after a single course of corticosteroids. *Pediatr Infect Dis J* 1990;9:729-32.

Kemp JP, Furukawa CT, Bronsky EA, et al. Albuterol treatment for children with asthma: a comparison of inhaled powder and aerosol. *J Allergy Clin Immunol* 1989;83:697-702.

Kerrebijn KF, van Essen-Zandvliet EE, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. *J Allergy Clin Immunol* 1987;79(4):653-9.

Kerstjens HA, Brand PL, Hughes MD, et al. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. *N Engl J Med* 1992;327:1413-9.

Kesten S, Ellas M, Cartier A, Chapman KR. Patient handling of a multidose dry powder inhalation device for albuterol. *Chest* 1994;105:1077-81.

Kidney J, Dominguez M, Taylor PM, Rose M, Chung KF, Barnes PJ. Immunomodulation by theophylline in asthma. *Am J Respir Crit Care Med* 1995;151:1907-14.

Kim CS, Eldridge MA, Sackner MA. Oropharyngeal deposition and delivery aspects of metered-dose inhaler aerosols. *Am Rev Respir Dis* 1987;135:157-64.

Klaustermeyer WB, Noritake DT, Kwong FK. Chrysotherpay in the treatment of corticosteroid-dependent asthma. *J Allergy Clin Immunol* 1987;79:720-5.

Kleijnen J, ter Riet G, Knipschild P. Acupuncture and asthma: a review of controlled trials. *Thorax* 1991;46:799-802.

Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a beta$_2$-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. *J Allergy Clin Immunol* 1992;90:32-42.

Laitinen LA, Laitinen A, Haino M, Haahtela T. Eosinophilic airway inflammation during exacerbation of asthma and its treatment with inhaled corticosteroid. *Am Rev Respir Dis* 1991;143(2):423-7.

Lal S, Dorow PD, Venho KK, Chatterjee SS. Nedocromil sodium is more effective than cromolyn sodium for the treatment of chronic reversible obstructive airway disease. *Chest* 1993;104:438-47.

Levy J, Zalkinder I, Kuperman O, et al. Effect of prolonged use of inhaled steroids on the cellular immunity of children with asthma. *J Allergy Clin Immunol* 1995;95:806-12.

Lipworth BJ. New perspectives on inhaled drug delivery and systemic bioactivity. *Thorax* 1995;50:105- 10.

Lotvall J, Lunde H, Ullman A, Tornqvist H, Svedmyr N. Twelve months treatment with inhaled salmeterol in asthmatic patients. Effects on beta$_2$-receptor function and inflammatory cells. *Allergy* 1992;47:477-83.

Lundback B, Rawlinson DW, Palmer JB. Twelve month comparison of salmeterol and salbutamol as dry powder formulations in asthmatic patients. European Study Group. *Thorax* 1993;48(2):148-53.

Maesen FP, Smeets JJ, Gubbelmans HL, Zwieers PG. Formoterol in the treatment of nocturnal asthma. *Chest* 1990;98:856-70.

Mann RD, Kubota K, Pearce G Wilton L. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemiol* 1996;49(2):247-50.

Mazer BD, Gelfand EW. An open-label study of high-dose intravenous immunoglobin in severe childhood asthma. *J Allergy Clin Immunol* 1991;87:976-83.

McFadden ER Jr. Perspectives in beta$_2$-agonist therapy: vox clamantis in deserto vel lux in tenebris? *J Allergy Clin Immunol* 1995;95:641-51.

McGill KA, Joseph B, Busse WW. Corticosteroids in the treatment of asthma. Practical recommendations. *Clin Immunother* 1995;4:16-48.

Melchor R, Biddiscombe MF, Mak VHF, Short MD, Spiro SG. Lung deposition patterns of directly labelled salbutamol in normal subjects and in patients with reversible airflow obstruction. *Thorax* 1993;48:506-11.

Meltzer SS, Hasday JD, Cohn J, Bleecker ER. Inhibition of exercise-induced bronchospasm by zileuton: a 5-lipoxygenase inhibitor. *Am J Respir Crit Care Med* 1996;153:931-5.

Morice A. Adulterated "homeopathic" care for asthma. *Lancet* 1986;1:862-3.

Multarkey ME, Blumenstein BA, Andrade WP, Bailey GA, Olason I, Wetzel CE. Methotrexate in the treatment of corticosteroid-dependent asthma. *N Engl J Med* 1988;318:603-7.

Mullen ML, Mullan B, Carey M. The association between beta$_2$-agonist use and death from asthma. *JAMA* 1993;270:1842-5.

Muranaka M, Miyamoto T, Shida T, et al. Gold salt in the treatment of bronchial asthma—a double-blind study. *Ann Allergy* 1978;40:132-7.

Nelson HS, Hamilos DL, Corsello PR, Lavesque NV, Buchmeier AD, Bucher BL. A double-blind study of troleandomycin and methylprednisolone in asthmatic subjects who require daily corticosteroids. *Am Rev Respir Dis* 1993;147:398-404.

Newhouse MT, Dolovich MB. Control of asthma by aerosols. *N Engl J Med* 1986;315:870-4.

Newman KB, Mason UG, Buchmeier A, Schmeling KB, Corsello P, Nelson HS. Failure of colchicine to reduce inhaled triamcinolone in patients with asthama. *J Allergy Clin Immunol* 1997;99:176-8.

Newman SP, Millar AB, Lennard-Jones TR, Moren F, Clarke SW. Improvement of pressurized aerosol deposition with Nebuhaler spacer device. *Thorax* 1984;39:935-41.

Newman SP, Moren F, Pavia D, Little F, Clarke SW. Deposition of pressurized suspension aerosols inhaled through extension devices. *Am Rev Respir Dis* 1981;124:317-20.

Newman SP, Weisz AWB, Talaee N, Clarke SW. Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. *Thorax* 1991;46:712-6.

Ninan TK, Russell G. Asthma, inhaled corticosteroid treatment, and growth. *Arch Dis Child* 1992;67(6):703-5.

Noonan M, Chervinsky P, Busse WW, et al. Fluticasone propionate reduces oral prednisone use while it improves asthma control and quality of life. *Am J Respir Crit Care Med* 1995;152:1467-73.

Novembre G, Frongia GF, Vanaruso G, Vierucci A. Inhibition of exercise-induced asthma (EIA) by nedocromil sodium and sodium cromoglycate in children. *Pediatr Allergy Immunol* 1994;5:107-10.

O'Callaghan C, Cant M, Robertson C. Delivery of beclomethasone dipropionate from a spacer device: what dose is available for inhalation? *Thorax* 1994;49:961-4.

O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the non-bronchodilator effects of inhaled beta$_2$-agonists in asthma. *N Engl J Med* 1992;327:1204-8.

O'Hickey SP, Rees PJ. High-dose nedocromil sodium as an addition to inhaled corticosteroids in the treatment of asthma. *Respir Med* 1994;88:499-502.

Packe GE, Douglas JG, McDonald AF, Robins SP, Reid DM. Bone density in asthmatic patients taking high dose inhaled beclomethasone dipropionate and intermittent systemic corticosteroids. *Thorax* 1992;47(6):414-7.

Pauwels RA. New aspects of the therapeutic potential of theophylline in asthma. *J Allergy Clin Immunol* 1989;83:548-53.

Pearlman DS, Chervinsky P, LaForce C, et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. *N Engl J Med* 1992;327:1420-5.

Pedersen S, Mortensen S. Use of different inhalation devices in children. *Lung* 1990;168(Suppl):653-7.

Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. *Arch Dis Child* 1990;65:308-10.

Pedersen S, Hansen OR. Budesonide treatment of moderate and severe asthma in children: a dose-response study. *J Allergy Clin Immunol* 1995;95:29-33.

Pincus DJ, Szefler SJ, Ackerson LM, Martin RJ. Chronotherpay of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. *J Allergy Clin Immunol* 1995;95:1172-8.

Pouw EM, Prummel MF, Oosting H, Roos CM, Endert E. Beclomethasone inhalation decreases serum osteocalcin concentrations. *BMJ* 1991;302:627-8.

Prahl P. Adrenocortical suppression following treatment with beclomethasone dipropionate and budesonide. *Clin Exp Allergy* 1991;21:145-6.

Prahl P, Janson T. Decreased adrenocortical suppression utilizing the nebuhaler for inhalation of steroid aerosols. *Clin Allergy* 1987;17:393-8.

Puolijoki H, Lilppo K, Herrala J, Saimi J, Tala E. Inhaled beclomethasone decreases serum osteocalcin in postmenopausal asthmatic women. *Bone* 1992;13(4):285-8.

Rafferty P, Tucker LG, Frame MH, Fergusson RJ, Biggs BA, Crompton GK. Comparison of budesonide and beclomethasone dipropionate in patients with severe chronic asthma: assessment of relative prednisolone-sparing effects. *Br J Dis Chest* 1985;79:244-50.

Ramage L, Lipworth BJ, Ingram CG, Cree IA, Dhillon DP. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. *Respir Med* 1994;88(5):363-8.

Reilly DT, McSharry C, Taylor MA, Aitchison T. Is homeopathy a placebo response? Controlled trial of homeopathic potency, with pollen in hayfever as model. *Lancet* 1986;2:881-6.

Rinehart JJ, Sagone AL, Balcerzak SP, Ackerman GA, LoBuglio AF. Effects of corticosteroid therapy on human monocyte function. *N Engl J Med* 1975;292:236-41.

Rooklin AR, Lampert SI, Jaeger EA, McGeady SJ, Mansmann HC Jr. Posterior subcapsular cataracts in steroid-requiring asthmatic children. *J Allergy Clin Immunol* 1979;63(6):383-6.

Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden ER Jr. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. *Am Rev Respir Dis* 1980;122:365-71.

Rowe BH, Keller JL, Oxman AD. Effectiveness of steroid therapy in acute exacerbations of asthma: a meta-analysis. *Am J Emerg Med* 1992;10:301-10.

Ruggins NR, Milner AD, Swarbrick A. An assessment of a new breath actuated inhaler device in acutely wheezy children. *Arch Dis Child* 1993;68:477-80.

Scarfone RJ, Fuchs SM, Nager AL, Shane SA. Controlled trial of oral prednisone in the emergency department treatment of children with acute asthma. *Pediatrics* 1993;2:513-8.

Schecker MH, Wilson AF, Mukal DS, Hahn M, Crook D, Novey HS. A device for overcoming discoordination with metered-dose inhalers. *J Allergy Clin Immunol* 1993;92:783-9.

Schwartz HJ, Blumenthal M, Brady R, et al. A comparative study of the clinical efficacy of nedocromil sodium and placebo. *Chest* 1996;109:945-52.

Sears MR, Taylor DR, Print CG, et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;336:1391-6.

Selroos O, Pietinalho A, Lofroos A, Riska H. Effect of early vs. late intervention with inhaled corticosteroids in asthma. *Chest* 1995;108:1228-34.

Selroos O, Halme M. Effect of a volumatic spacer and mouth rinsing on systemic absorption of inhaled corticosteroids from a metered dose inhaler and dry powder inhaler. *Thorax* 1991;46:891-4.

Shaw NJ, Edmunds AT. Inhaled beclomethasone and oral candidiasis. *Arch Dis Child* 1986;61:788-90.

Shiner RJ, Nunn AJ, Chung KF, Gedder DM. Randomised, double-blind, placebo-controlled trial of methotrexate in steroid-dependent asthma. *Lancet* 1990;336:137-40.

Stik HJ, Guay-Woodford L, Perez-Atayde AR, Geha RS, Broff MD. Fatal *varicella* in steroid-dependent asthma. *J Allergy Clin Immunol* 1988;81:47-51.

Simons FE, Persaud MP, Gillespie CA, Cheang M, Shuckett EP. Absence of posterior subcapsular cataracts in young patients treated with inhaled glucocorticoids. *Lancet* 1993;342:776-8.

Spector SL, Smith LJ, Glass M. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D4 receptor antagonist, in subjects with bronchial asthma. *Am J Respir Crit Care Med* 1994;150:618-23.

Spitzer WO, Suissa S, Ernst P, et al. The use of beta-agonist and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501-6.

Storms WW, Bodman SF, Nathan RA, et al. Use of ipratropium bromide in asthma. *Am J Med* 1986;81:61-6.

Suissa S, Ernst P, Boivin JP, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994;149:604-10.

Sullivan P, Bekir S, Jaffar Z, Page C, Jeffrey P, Costello J. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma. *Lancet* 1994;343:1006-8.

Svendsen UG, Jorgensen H. Inhaled nedocromil sodium as additional treatment to high dose inhaled corticosteroids in the management of bronchial asthma. *Eur Respir J* 1991;4:992-9.

Tabachnik E, Zadik Z. Diurnal cortisol secretion during therapy with inhaled beclomethasone dipropionate in children with asthma. *J Pediatr* 1991;118:294-7.

Taylor IK, O'Shaughenessy KM, Fuller RW, Dollery CT. Effect of cysteinyl-leukotriene receptor antagonist ICI 204,219 on allergen-induced bronchoconstriction and airway hyperreactivity in atopic subjects. *Lancet* 1991;337:690-4.

Thompson NC. Nedocromil sodium: an overview. *Respir Med* 1989;83:269-76.

Thorsson L, Edsbacker S, Conradson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. *Eur Respir J* 1994;7:1839-44.

Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92:64-77.

Toogood JH, Jennings B, Greenway RW, Chuang L. Candidiasis and dysphonia complicating beclomethasone treatment of asthma. *J Allergy Clin Immunol* 1980;65:145-53.

Toogood JH, Baskerville JC, Markov AE, et al. Bone mineral density and the risk of fracture in patients receiving long-term inhaled steroid therapy for asthma. *J Allergy Clin Immunol* 1995;96:157-66.

Toogood JH, Crilly RG, Jones G, Nadeau J, Wells GA. Effect of high-dose inhaled budesonide on calcium and phosphate metabolism and the risk of osteoporosis. *Am Rev Respir Dis* 1988;138(1):57-61.

Toogood JH, Jennings B, Hodsman AB, Baskerville J, Fraher LJ. Effects of dose and dosing schedule of inhaled budesonide on bone turnover. *J Allergy Clin Immunol* 1991;88:572-80.

Toogood JH, Markov AE, Baskerville J, Dyson C. Association of ocular cataracts with inhaled and oral steroid therapy during long-term treatment of asthma. *J Allergy Clin Immunol* 1993;91:571-9.

Turpeinen M, Sorva R, Juntunen-Backman K. Changes in carbohydrate and lipid metabolism in children with asthma inhaling budesonide. *J Allergy Clin Immunol* 1991;88:384-9.

Ullman A, Hedner J, Svedmyr N. Inhaled salmeterol and salbutamol in asthmatic patients. An evaluation of asthma symptoms and the possible development of tachyphylaxis. *Am Rev Respir Dis* 1990;142:571-5.

van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and/or beta$_2$-agonists on lung function, airway responsiveness, and symptoms in children with asthma. *Am Rev Respir Dis* 1992;146:547-54.

van Schayck CP, Dompeling E, van Herwaarden CL, et al. Bronchodilator treatment in moderate asthma or chronic bronchitis: continuous or on demand? A randomized controlled study. *BMJ* 1991;303:1426-31.

Vidgren M, Karkkäinen A, Karjalainen P, Nuutinen J, Paronen P. In vitro and in vivo deposition of drug particles from pressurized aerosol and dry powder inhaler. *Drug Devel Indust Pharm* 1983;14:2649-65.

Weinberger M, Hendeles L. Theophylline in asthma. *N Engl J Med* 1996;334:1380-8.

Wolthers OD. Long-, intermediate- and short-term growth studies in asthmatic children treated with inhaled glucocorticosteroids. *Eur Respir J* 1996;9:821-7.

Wong CS, Cooper S, Britton JR, Tattersfield AE. Steroid sparing effect of nedocromil sodium in asthmatic patients on high doses of inhaled steroids. *Clin Exp Allergy* 1993;23:370-6.

Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroid. *Am J Respir Crit Care Med* 1996;153:1481-8.

Yates DH, Sussman HS, Shaw MJ, Barnes PJ, Chung KF. Regular formoterol treatment in mild asthma. Effect on bronchial responsiveness during and after treatment. *Am J Respir Crit Care Med* 1995;152:1170-4.

Ziment I, Stein M. Inappropriate and unusual remedies. In: Weiss EB, Stein M, eds. *Bronchial Asthma*. Boston: Little, Brown and Company, 1993, pp. 1145-51.

Pharmacologic Therapy: Managing Asthma Long Term

KEY RECOMMENDATIONS FOR MANAGING ASTHMA LONG TERM

- Persistent asthma is most effectively controlled with daily long-term-control medication, specifically, anti-inflammatory therapy.
- A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma:
  - The amount and frequency of medication is dictated by asthma severity and directed toward suppression of airway inflammation.
  - Therapy should be initiated at a higher level than the patient's step of severity at the onset to establish prompt control and then stepped down.
  - Continual monitoring is essential to ensure that asthma control is achieved.
  - Step-down therapy is essential to identify the minimum medication necessary to maintain control.
- Regular followup visits (at 1- to 6-month intervals) are essential to ensure that control is maintained and the appropriate step down in therapy is considered.
- Therapeutic strategies should be considered in concert with clinician-patient partnership strategies; education of patients is essential for achieving optimal pharmacologic therapy.
- At each step, patients should be advised to avoid or control allergens, irritants, or other factors that make the patient's asthma worse.
- Referral to an asthma specialist for consultation or comanagement of the patient is recommended if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care (see component 1-Initial Assessment and Diagnosis). Referral may be considered if the patient requires step 3 care. For infants and young children, referral is recommended if the patient requires step 3 or 4 care and should be considered if the patient requires step 2 care.

STEPWISE APPROACH FOR MANAGING ASTHMA IN ADULTS AND CHILDREN OLDER THAN 5 YEARS OF AGE

The aim of asthma therapy is to maintain control of asthma with the least amount of medication and hence minimal risk for adverse effects. Control of asthma is defined as:

- Preventing chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
- Maintaining (near) "normal" pulmonary function
- Maintaining normal activity levels (including exercise and other physical activity)
- Preventing recurrent exacerbations of asthma and minimizing the need for emergency department visits or hospitalizations
- Providing optimal pharmacotherapy with minimal or no adverse effects
- Meeting patients' and families' expectations of and satisfaction with asthma care

The stepwise approach to therapy, in which the dose and number of medications and frequency of administration are increased as necessary and decreased when possible, is used to achieve this control. This is illustrated in figures 3-4a and 3-4b. Figures 3-5a and 3-5d present usual medication dosages for therapy. Because asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations, therapy for persistent asthma must emphasize efforts to suppress inflammation over the long term and prevent exacerbations. Recommendations in the stepwise approach to therapy are based on the Expert Panel's review of the literature (see component 3-Medications) and the Expert Panel's experience and opinion.

Gaining Control of Asthma

The clinician must judge individual patient needs and circumstances to determine at what step to initiate therapy. There are two appropriate approaches to gaining control of asthma:

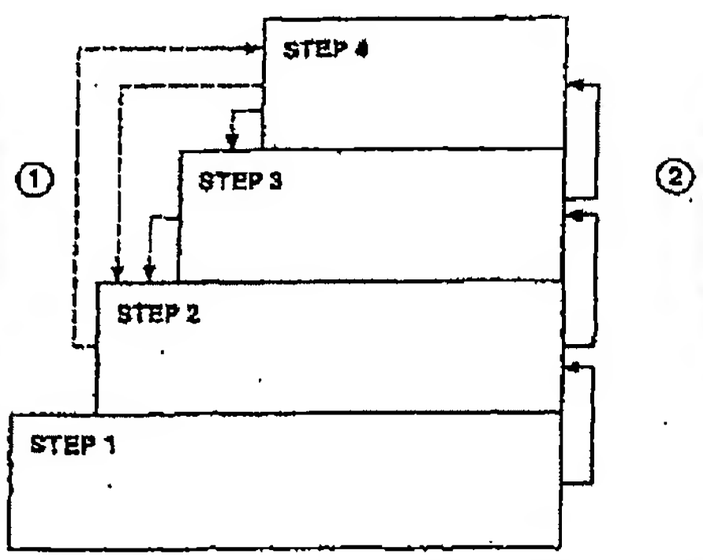
- Start treatment at the step appropriate to the severity of the patient's disease at the time of evaluation and gradually step up if control is not achieved.

OR

- At the onset, administer therapy at a level higher than the patient's step of severity to gain rapid control. This can be accomplished by either a short course of systemic corticosteroids (see figure 3-5a) along with inhaled corticosteroids or initiating a medium-to-high dose of inhaled corticosteroids. Once control is gained, step down the therapy.

The two approaches are illustrated by the solid and broken lines in the following diagram.

TWO APPROACHES TO GAINING CONTROL OF ASTHMA: (1) START WITH HIGH-DOSE THERAPY AND STEP DOWN OR (2) GRADUALLY STEP UP THERAPY



The more aggressive approach of gaining prompt control with a higher level of therapy is preferred, in the opinion of the Expert Panel. At present, there are no studies directly comparing the two approaches—the traditional step-up care (low dose to high) vs. step-down care (initial high dose to low). However, there is evidence supporting a more aggressive initial approach. First, asthma symptoms and altered pulmonary function are related to the level of ongoing airway inflammation. Suppression of airway inflammation is more likely to occur with higher doses of corticosteroids. Furthermore, studies indicate that the dose of inhaled or systemic corticosteroids can be reduced and the clinical benefits sustained once the disease is controlled (Haahtela et al. 1994; Agertoft and Pedersen 1994). A preliminary observation in a retrospective study of children suggests that initiating inhaled corticosteroids early in the course of the disease results in better clinical benefit and less accumulated corticosteroid dose over the long term (Agertoft and Pedersen 1994). Therefore, it is conceivable that a more aggressive approach in initial therapy will more rapidly suppress airway inflammation, restore pulmonary function, and allow for eventual asthma control at lower doses of anti-inflammatory therapy.

Continual monitoring is essential to ensure that asthma control is achieved. Control is indicated by, for example, peak expiratory flow (PEF) values indicating less than 10 to 20 percent variability or PEF consistently greater than 80 percent of the patient's personal best, minimal symptoms, minimal need for short-acting inhaled $beta_2$-agonist, absence of nighttime awakenings, and no activity limitations.

If control is not achieved with initial therapy (e.g., within 1 month), the pharmacologic management plan, and possibly the diagnosis, should be reevaluated (see Pharmacologic Steps, page 87).

Maintaining Control of Asthma

Once control is achieved and sustained for several weeks or months, a reduction in pharmacologic therapy—a step down—is appropriate and helpful to identify the minimum therapy for maintaining control. Reduction in therapy should be gradual because asthma can deteriorate at a highly variable rate and intensity.

In general, the last medication added to the medical regimen should be the first medication reduced. Although guidelines for the rate of reduction and intervals for evaluation have not been established, the opinion of the Expert Panel is that the dose of inhaled corticosteroids may be reduced about

FIGURE 3-4a. STEPWISE APPROACH FOR MANAGING ASTHMA IN ADULTS AND CHILDREN OLDER THAN 6 YEARS OF AGE

Goals of Asthma Treatment

- Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
- Maintain (near) "normal" pulmonary function
- Maintain normal activity levels (including exercise and other physical activity)
- Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meet patients' and families' expectations of and satisfaction with asthma care

Classify Severity of Asthma	Clinical Features Before Treatment*		
	Symptoms**	Nighttime Symptoms	Lung Function
STEP 4 Severe Persistent	▪ Continual symptoms ▪ Limited physical activity ▪ Frequent exacerbations	Frequent	▪ FEV_1 or PEF ≤60% predicted ▪ PEF variability >30%
STEP 3 Moderate Persistent	▪ Daily symptoms ▪ Daily use of inhaled short-acting $beta_2$-agonist ▪ Exacerbations affect activity ▪ Exacerbations ≥2 times a week; may last days	>1 time a week	▪ FEV_1 or PEF >60% –<80% predicted ▪ PEF variability >30%
STEP 2 Mild Persistent	▪ Symptoms >2 times a week but <1 time a day ▪ Exacerbations may affect activity	>2 times a month	▪ FEV_1 or PEF ≥80% predicted ▪ PEF variability 20–30%
STEP 1 Mild Intermittent	▪ Symptoms ≤2 times a week ▪ Asymptomatic and normal PEF between exacerbations ▪ Exacerbations brief (from a few hours to a few days); intensity may vary	≤2 times a month	▪ FEV_1 or PEF ≥80% predicted ▪ PEF variability <20%

* The presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. The characteristics noted in this figure are general and may overlap because asthma is highly variable. Furthermore, an individual's classification may change over time.

** Patients at any level of severity can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.

FIGURE 3-4b. STEPWISE APPROACH FOR MANAGING ASTHMA IN ADULTS AND CHILDREN OLDER THAN 5 YEARS OF AGE: TREATMENT

Preferred treatments are in bold print.

	Long-Term Control	Quick Relief	Education
STEP 4 Severe Persistent	Daily medications: ▪ Anti-inflammatory: inhaled corticosteroid (high dose) AND ▪ Long-acting bronchodilator: either long-acting inhaled beta$_2$-agonist, sustained-release theophylline, or long-acting beta$_2$-agonist tablets AND ▪ Corticosteroid tablets or syrup long term (make repeat attempts to reduce systemic steroids and maintain control with high dose inhaled steroids)	▪ Short-acting bronchodilator: inhaled beta$_2$-agonists as needed for symptoms. ▪ Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. ▪ Use of short-acting inhaled beta$_2$-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.	Steps 2 and 3 actions plus: ▪ Refer to individual education/counseling
STEP 3 Moderate Persistent	Daily medication: ▪ Either Anti-inflammatory: inhaled corticosteroid (medium dose) OR Inhaled corticosteroid (low-medium dose) and add a long-acting bronchodilator, especially for nighttime symptoms; either long-acting inhaled beta$_2$-agonist, sustained-release theophylline, or long-acting beta$_2$-agonist tablets. ▪ If needed Anti-inflammatory: inhaled corticosteroids (medium-high dose) AND Long-acting bronchodilator, especially for nighttime symptoms; either long-acting inhaled beta$_2$-agonist, sustained-release theophylline, or long-acting beta$_2$-agonist tablets.	▪ Short-acting bronchodilator: inhaled beta$_2$-agonists as needed for symptoms. ▪ Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. ▪ Use of short-acting inhaled beta$_2$-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.	Step 1 actions plus: ▪ Teach self-monitoring ▪ Refer to group education if available ▪ Review and update self-management plan

FIGURE 3-4b. STEPWISE APPROACH FOR MANAGING ASTHMA IN ADULTS AND CHILDREN OLDER THAN 5 YEARS OF AGE: TREATMENT (CONTINUED)

Preferred treatments are in bold print.

	Long-Term Control	Quick Relief	Education
STEP 2 Mild Persistent	One daily medication: ▪ Anti-inflammatory: either inhaled corticosteroid (low doses) or cromolyn or nedocromil (children usually begin with a trial of cromolyn or nedocromil). ▪ Sustained-release theophylline to serum concentration of 5-15 mcg/mL is an alternative, but not preferred, therapy. Zafirlukast or zileuton may also be considered for patients ≥12 years of age, although their position in therapy is not fully established.	▪ Short-acting bronchodilator: inhaled beta$_2$-agonists as needed for symptoms. ▪ Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. ▪ Use of short-acting inhaled beta$_2$-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.	Step 1 actions plus: ▪ Teach self-monitoring ▪ Refer to group education if available ▪ Review and update self-management plan
STEP 1 Mild Intermittent	▪ No daily medication needed.	▪ Short-acting bronchodilator: inhaled beta$_2$-agonists as needed for symptoms. ▪ Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. ▪ Use of short-acting inhaled beta$_2$-agonists more than 2 times a week may indicate the need to initiate long-term-control therapy.	▪ Teach basic facts about asthma ▪ Teach inhaler/spacer/holding chamber technique ▪ Discuss roles of medications ▪ Develop self-management plan ▪ Develop action plan for when and how to take rescue actions, especially for patients with a history of severe exacerbations ▪ Discuss appropriate environmental control measures to avoid exposure to known allergens and irritants (See component 4.)

↓ **Step down**
Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.

↑ **Step up**
If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control (avoidance of allergens or other factors that contribute to asthma severity).

NOTE:

- The stepwise approach presents general guidelines to assist clinical decisionmaking; it is not intended to be a specific prescription. Asthma is highly variable; clinicians should tailor specific medication plans to the needs and circumstances of individual patients.
- Gain control as quickly as possible; then decrease treatment to the least medication necessary to maintain control. Gaining control may be accomplished by either starting treatment at the step most appropriate to the initial severity of the condition or starting at a higher level of therapy (e.g., a course of systemic corticosteroids or higher dose of inhaled corticosteroids).
- A rescue course of systemic corticosteroids may be needed at any time and at any step.
- Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms. This may be especially common with exacerbations provoked by respiratory infections. A short course of systemic corticosteroids is recommended.
- At each step, patients should control their environment to avoid or control factors that make their asthma worse (e.g., allergens, irritants); this requires specific diagnosis and education.
- Referral to an asthma specialist for consultation or comanagement is *recommended* if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care. Referral *may be considered* if the patient requires step 3 care (see also components 1-Initial Assessment and Diagnosis).

FIGURE 3-5a. USUAL DOSAGES FOR LONG-TERM-CONTROL MEDICATIONS

Medication	Dosage Form	Adult Dose	Child Dose	Comments
Inhaled Corticosteroids (see figures 3-5b and 3-5c)				
Systemic Corticosteroids			(Applies to all three systemic corticosteroids)	
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	▪ 7.5–60 mg daily in a single dose or qod as needed for control ▪ Short-course "burst": 40–60 mg per day as single or 2 divided doses for 3–10 days	▪ 0.25–2 mg/kg daily in single dose or qod as needed for control ▪ Short course "burst": 1–2 mg/kg/day, maximum 60 mg/day, for 3–10 days	▪ For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression). If daily doses are required, one study suggests improved efficacy and no increase in adrenal suppression when administered at 3:00 p.m. (Beam et al, 1992). ▪ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. ▪ The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3-10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
Prednisolone	5 mg tablets, 5 mg/5 cc, 15mg/5 cc			
Prednisone	1, 2.5, 5, 10, 20, 25 mg tablets; 5 mg/cc, 5 mg/5 cc			
Cromolyn and Nedocromil				
Cromolyn	MDI 1 mg/puff Nebulizer solution 20 mg/ampule	2–4 puffs tid-qid 1 ampule tid-qid	1–2 puffs tid-qid 1 ampule tid-qid	▪ One dose prior to exercise or allergen exposure provides effective prophylaxis for 1–2 hours.
Nedocromil	MDI 1.75 mg/puff	2–4 puffs bid-qid	1–2 puffs bid-qid	▪ See cromolyn above.
Long-Acting Beta$_2$-Agonists				
Salmeterol	*Inhaled* MDI 21 mcg/puff, 60 or 120 puffs DPI 50 mcg/blister	2 puffs q 12 hours 1 blister q 12 hours	1–2 puffs q 12 hours 1 blister q 12 hours	▪ May use one dose nightly for symptoms. ▪ Should not be used for symptom relief or for exacerbations.
Sustained-Release Albuterol	*Tablet* 4 mg tablet	4 mg q 12 hours	0.3–0.6 mg/kg/day, not to exceed 8 mg/day	
Methylxanthines				
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg max; usual max 800 mg/day	Starting dose 10 mg/kg/day; usual max: ▪ <1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day ▪ ≥1 year of age: 16 mg/kg/day	▪ Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady-state (at least 48 hours on same dosage). ▪ Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is important. ▪ See factors on page 87 that can affect levels.
Leukotriene Modifiers				
Zafirlukast	20 mg tablet	40 mg daily (1 tablet bid)		▪ For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ▪ For zileuton, monitor hepatic enzymes (ALT).
Zileuton	300 mg tablet 600 mg tablet	2,400 mg daily (two 300 mg tablets or one 600 mg tablet, qid)		

FIGURE 3-5a. USUAL DOSAGES FOR LONG-TERM-CONTROL MEDICATIONS (CONTINUED)

Factors Affecting Serum Theophylline Concentrations*

Factor	Decreases Theophylline Concentrations	Increases Theophylline Concentrations	Recommended Action
Food	↓ or delays absorption of some sustained-release theophylline (SRT) products	↑ rate of absorption (fatty foods) products	Select theophylline preparation that is not affected by food..
Diet	↑ metabolism (high protein)	↓ metabolism (high carbohydrate)	Inform patients that major changes in diet are not recommended while taking theophylline.
Systemic, febrile viral illness (e.g., influenza)		↓ metabolism	Decrease theophylline dose according to serum concentration level. Decrease dose by 50 percent if serum concentration measurement is not available.
Hypoxia, cor pulmonale, and decompensated congestive heart failure, cirrhosis		↓ metabolism	Decrease dose according to serum concentration level.
Age	↑ metabolism (1 to 9 years)	↓ metabolism (<6 months, elderly)	Adjust dose according to serum concentration level.
Phenobarbital, phenytoin, carbamazepine	↑ metabolism		Increase dose according to serum concentration level.
Cimetidine		↓ metabolism	Use alternative H_2 blocker (e.g., famotidine or ranitidine).
Macrolides: TAO, erythromycin, clarithromycin		↓ metabolism	Use alternative antibiotic or adjust theophylline dose.
Quinolones: ciprofloxacin, enoxacin, pefloxacin		↓ metabolism	Use alternative antibiotic or adjust theophylline dose. Circumvent with ofloxacin if quinolone therapy is required.
Rifampin	↑ metabolism		Increase dose according to serum concentration level.
Ticlopidine		↓ metabolism	Decrease dose according to serum concentration level.
Smoking	↑ metabolism		Advise patient to stop smoking; increase dose according to serum concentration level.

* This list is not all-inclusive; for discussion of other factors, see package inserts.

25 percent every 2 to 3 months to the lowest dose possible required to maintain control. It is likely that most patients with persistent asthma will continue to benefit from daily medication to suppress underlying airway inflammation. Patients may relapse when inhaled corticosteroids are completely discontinued (Waalkens et al. 1993).

Regular followup visits (at 1- to 6-month intervals) are essential. Clinicians need to assess whether control of asthma has been maintained and if a step down in therapy is appropriate. Clinicians also need to monitor and review the daily self-management and action plans, the medications, and the patient's self-management behaviors (e.g., inhaler and peak flow monitoring techniques, actions to control factors that aggravate their asthma) (see figure 4-2).

The Expert Panel *recommends* referral to an asthma specialist for consultation or comanagement of the patient if: there are difficulties achieving or maintaining control of asthma; immunotherapy is being considered; the patient requires step 4 care (step 3 or 4 care for infants and young children); or the patient has had a life-threatening exacerbation (see component 1-Initial Assessment and Diagnosis). Referral *may be considered* if a patient requires step 3 care (or step 2 care for infants and young children).

Pharmacologic Steps

The following recommendations for pharmacologic therapy at different steps of asthma severity (see figures 3-4a and 3-4b) are intended to be general guidelines for making therapeutic decisions. They are not

FIGURE 3-5b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS

Adults

Drug	Low Dose	Medium Dose	High Dose
Beclomethasone dipropionate 42 mcg/puff 84 mcg/puff	168-504 mcg (4-12 puffs — 42 mcg) (2-6 puffs — 84 mcg)	504-840 mcg (12-20 puffs — 42 mcg) (6-10 puffs — 84 mcg)	>840 mcg (>20 puffs — 42 mcg) (>10 puffs — 84 mcg)
Budesonide DPI: 200 mcg/dose	200-400 mcg (1-2 inhalations)	400-600 mcg (2-3 inhalations)	>600 mcg (>3 inhalations)
Flunisolide 250 mcg/puff	500-1,000 mcg (2-4 puffs)	1,000-2,000 mcg (4-8 puffs)	>2,000 mcg (>8 puffs)
Fluticasone MDI: 44, 110, 220 mcg/puff	88-264 mcg (2-6 puffs — 44 mcg) OR (2 puffs — 110 mcg)	264-660 mcg (2-6 puffs — 110 mcg)	>660 mcg (>6 puffs — 110 mcg) OR (>3 puffs — 220 mcg)
DPI: 50, 100, 250 mcg/dose	(2-6 inhalations — 50 mcg)	(3-6 inhalations — 100 mcg)	(>6 inhalations — 100 mcg) OR (>2 inhalations — 250 mcg)
Triamcinolone acetonide 100 mcg/puff	400-1,000 mcg (4-10 puffs)	1,000-2,000 mcg (10-20 puffs)	>2,000 mcg (>20 puffs)

Children

Drug	Low Dose	Medium Dose	High Dose
Beclomethasone dipropionate 42 mcg/puff 84 mcg/puff	84-336 mcg (2-8 puffs — 42 mcg) (1-4 puffs — 84 mcg)	336-672 mcg (8-16 puffs — 42 mcg) (4-8 puffs — 84 mcg)	>672 mcg (>16 puffs — 42 mcg) (>8 puffs — 84 mcg)
Budesonide DPI: 200 mcg/dose	100-200 mcg	200-400 mcg (1-2 inhalations — 200 mcg)	>400 mcg (>2 inhalations — 200 mcg)
Flunisolide 250 mcg/puff	500-750 mcg (2-3 puffs)	1,000-1,250 mcg (4-5 puffs)	>1,250 mcg (>5 puffs)
Fluticasone MDI: 44, 110, 220 mcg/puff	88-176 mcg (2-4 puffs — 44 mcg)	176-440 mcg (4-10 puffs — 44 mcg) OR (2-4 puffs — 110 mcg)	>440 mcg (>4 puffs — 110 mcg) OR (>2 puffs — 220 mcg)
DPI: 50, 100, 250 mcg/dose	(2-4 inhalations — 50 mcg)	(2-4 inhalations — 100 mcg)	(>4 inhalations — 100 mcg) OR (>2 inhalations — 250 mcg)
Triamcinolone acetonide 100 mcg/puff	400-800 mcg (4-8 puffs)	800-1,200 mcg (8-12 puffs)	>1,200 mcg (>12 puffs)

Note:

- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. The clinician must monitor the patient's response on several clinical parameters and adjust the dose accordingly. The stepwise approach to therapy emphasizes that once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effect.
- See figure 3-5c for an explanation of the rationale used for the comparative dosages. The reference point for the range in the dosages for children is data on the safety of inhaled corticosteroids in children, which, in general, suggest that the dose ranges are equivalent to beclomethasone dipropionate 200-400 mcg/day (low dose), 400-800 mcg/day (medium dose), and >800 mcg/day (high dose).
- Some dosages may be outside package labeling.
- Metered-dose inhaler (MDI) dosages are expressed as the actuator dose (the amount of drug leaving the actuator and delivered to the patient), which is the labeling required in the United States. This is different from the dosage expressed as the valve dose (the amount of drug leaving the valve, all of which is not available to the patient), which is used in many European countries and in some of the scientific literature. Dry powder inhaler (DPI) doses are expressed as the amount of drug in the inhaler following activation.

FIGURE 3-5c. ESTIMATED CLINICAL COMPARABILITY OF DOSES FOR INHALED CORTICOSTEROIDS

Data from in vitro and clinical trials suggest that the different inhaled corticosteroid preparations are not equivalent on a per puff or microgram basis. However, it is not entirely clear what implications these differences have for dosing recommendations in clinical practice because there are few data directly comparing the preparations. Relative dosing for clinical comparability is affected by differences in topical potency, clinical effects at different doses, delivery device, and bioavailability. *The Expert Panel developed recommended dose ranges (see figure 3-5b) for different preparations based on available data and the following assumptions and cautions about estimating relative doses needed to achieve comparable clinical effect.*

- Relative topical potency using human skin blanching
  - The standard test for determining relative topical anti-inflammatory potency is the topical vasoconstriction (MacKenzie skin blanching) test.
  - The MacKenzie topical skin blanching test correlates with binding affinities and binding half-lives for human lung corticosteroid receptors (see table below) (Dahlberg et al. 1994; Hogger and Rohdewald 1994).
  - The relationship between relative topical anti-inflammatory effect and clinical comparability in asthma management is not certain. However, recent clinical trials suggest that different in vitro measures of anti-inflammatory effect correlate with clinical efficacy (Barnes and Pedersen 1993; Johnson 1996; Kamada et al. 1996; Ebden et al. 1986; Leblanc et al. 1994; Gustafsson et al. 1993; Lundback et al. 1993; Barnes et al. 1993; Fabbri et al. 1993; Langdon and Capsey 1994; Ayres et al. 1995; Rafferty et al. 1985; Bjorkander et al. 1982; Sukss et al. 1982; Willey et al. 1982).

Medication	Topical Potency (Skin Blanching)*	Corticosteroid Receptor Binding Half-Life	Receptor Binding Affinity
Beclomethasone dipropionate (BDP)	600	7.5 hours	13.5
Budesonide (BUD)	980	5.1 hours	9.4
Flunisolide (FLU)	330	3.5 hours	1.8
Fluticasone propionate (FP)	1,200	10.5 hours	18.0
Triamcinolone acetonide (TAA)	330	3.9 hours	3.6

* Numbers are assigned in reference to dexamethasone, which has a value of "1" in the MacKenzie test.

- Relative doses to achieve similar clinical effects
  - Clinical effects are evaluated by a number of outcome parameters (e.g., changes in spirometry, peak flow rates, symptom scores, quick-relief beta$_2$-agonist use, frequency of exacerbations, airway responsiveness).
  - The daily dose and duration of treatment may affect these outcome parameters differently (e.g., symptoms and peak flow may improve at lower doses and over a shorter treatment time than bronchial reactivity) (van Essen-Zandvliet et al. 1992; Haahtela et al. 1991).
  - Delivery systems influence comparability. For example, the DPI delivery device for budesonide delivers approximately twice the amount of drug to the airway as the MDI, thus enhancing the clinical effect (Thorsson et al. 1994; Agertoft and Pedersen 1993).
  - *Individual patients may respond differently to different preparations, as noted by clinical experience.*

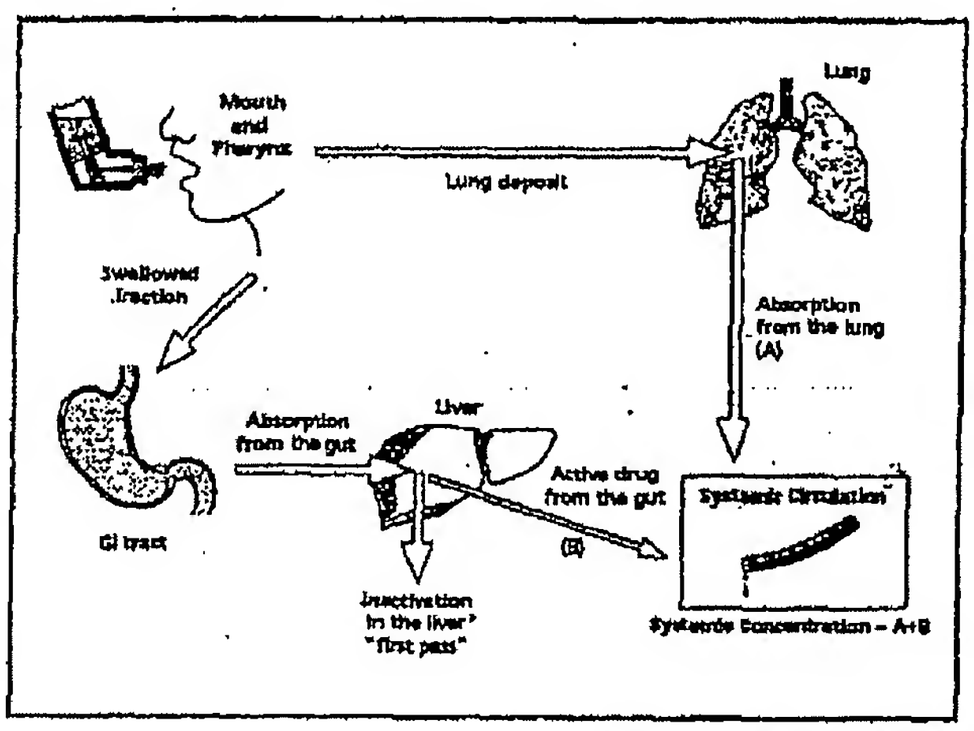
Clinical trials comparing effects in reducing symptoms and improving peak expiratory flow demonstrate:

- BDP and BUD achieved comparable effects at similar microgram doses by MDI (Bjorkander et al. 1982; Ebden et al. 1986; Rafferty et al. 1985).
- BDP achieved effects similar to twice the dose of TAA on a microgram basis.
- FP achieved effects similar to twice the dose of BDP and BUD via an MDI on a microgram basis (Gustaffson et al. 1993; Fabbri et al. 1993; Barnes et al. 1993; Dahl et al. 1993; Ayres et al. 1995).
- BUD by dry powder inhaler achieved effects similar to twice the dose delivered by MDI, thus implying greater bronchial delivery by the delivery device (Thorsson et al. 1994; Agertoft and Pedersen 1993).

FIGURE 3-5c. ESTIMATED CLINICAL COMPARABILITY OF DOSES FOR INHALED CORTICOSTEROIDS (CONTINUED)

- Bioavailability

Both the relative potency and the relative bioavailability (systemic availability) determine the potential for systemic activity of an inhaled corticosteroid preparation. As illustrated here, the bioavailability of an inhaled corticosteroid is dependent on the absorption of the dose delivered to the lungs and the oral bioavailability of the swallowed portion of the dose received.



Adapted with permission from Barnes 1995.

— Absorption of the dose delivered to the lungs:
  - Approximately 10 to 30 percent of the dose from the MDI is delivered to the lungs. This amount varies among preparations and delivery devices.
  - Nearly all of the amount delivered to the lungs is bioavailable.
— Oral bioavailability of the swallowed portion of the dose received:
  - Approximately 80 percent of the dose from the MDI without a spacer/holding chamber is swallowed.
  - The oral bioavailability of this amount varies:

    Either a high first-pass liver metabolism or the use of a spacer/holding chamber with an MDI can decrease oral bioavailability, thus enhancing safety (Lipworth 1995).

    The approximate oral bioavailability of inhaled corticosteroids has been reported as: BDP 20%; FLU 21%; TAA 10.6%; BUD 11%; FP 1% (Chaplin et al. 1980; Check and Kallner 1990; Clissold and Heel 1984; Davies 1993; Harding 1990; Heald et al. 1995; Martin et al. 1974; Mollman et al. 1985; Szefler 1991; Wurthwein and Rohdewald 1990).

Although few clinical trials are available that compare systemic activity among preparations (Kamada et al. 1996), studies have found:

— As suggested by one cross-over comparison study, BDP, FLU, and TAA appear to have equivalent dose-dependent systemic activity, as measured by 24-hour urinary free cortisol excretion (McCubbin et al. 1995).
— Inconsistent results comparing BDP and BUD. Some show equivalent systemic activity (Kamada et al. 1996; Prahl 1991; Prahl et al. 1987); others show BUD having slightly less systemic activity than BDP (Barnes and Pedersen 1993; Pedersen and Fuglsang 1988; Bisgaard et al. 1988).
— FP had greater adrenal suppression at doses of 400 to 2,000 micrograms than BUD in equivalent microgram doses delivered by MDI and accompanied by mouth washing to prevent oral bioavailability (Clark et al. 1996). This confirms that there are differences in microgram potencies among preparations and that absorption through the lung can result in systemic activity.

FIGURE 3-5d. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS

Medication	Dosage Form	Adult Dose	Child Dose	Comments
Short-Acting Inhaled Beta$_2$-Agonists				
Albuterol Albuterol HFA Bitolterol Pirbuterol Terbutaline	*MDI* 90 mcg/puff, 200 puffs 90 mcg/puff, 200 puffs 370 mcg/puff, 300 puffs 200 mcg/puff, 400 puffs 200 mcg/puff, 300 puffs	▪ 2 puffs 5 minutes prior to exercise ▪ 2 puffs tid-qid prn	▪ 1-2 puffs 5 minutes prior to exercise ▪ 2 puffs tid-qid prn	▪ An increasing use or lack of expected effect indicates diminished control of asthma. ▪ Not generally recommended for long-term treatment. Regular use on a daily basis indicates the need for additional long-term-control therapy. ▪ Differences in potency exist so that all products are essentially equipotent on a per puff basis. ▪ May double usual dose for mild exacerbations. ▪ Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessivecardiac stimulation, especially in high doses.
Albuterol Rotahaler	*DPI* 200 mcg/capsule	1-2 capsules q 4-6 hours as needed and prior to exercise	1 capsule q 4-6 hours as needed and prior to exercise	
Albuterol	*Nebulizer solution* 5 mg/mL (0.5%)	1.25-5 mg (.25-1 cc) in 2-3 cc of saline q 4-8 hours	0.05 mg/kg (min 1.25 mg, max 2.5 mg) in 2-3 cc of saline q 4-6 hours	May mix with cromolyn or ipratropium nebulizer solutions. May double dose for mild exacerbations.
Bitolterol	2 mg/mL (0.2%)	0.5-3.5mg (.25-1 cc) in 2-3 cc of saline q 4-8 hours	Not established	May not mix with other nebulizer solutions.
Anticholinergics				
Ipratropium	*MDI* 18 mcg/puff, 200 puffs	2-3 puffs q 6 hours	1-2 puffs q 6 hours	Evidence is lacking for anticholinergics producing added benefit to beta$_2$-agonists in long-term asthma therapy.
	Nebulizer solution .25 mg/mL (0.025%)	0.25 mg q 6 hours	0.25-0.5 mg q 6 hours	
Systemic Corticosteroids		(Applies to all three systemic corticosteroids)		
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	▪ Short course "burst": 40-60 mg/day as single or 2 divided doses for 3-10 days	▪ Short course "burst": 1-2 mg/kg/day, maximum 60 mg/day, for 3-10 days	▪ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. ▪ The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3-10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
Prednisolone	5 mg tabs; 5 mg/5 cc, 15 mg/5 cc			
Prednisone	1, 2.5, 5, 10, 20, 25 mg tabs; 5 mg/cc, 5 mg/5 cc			

Intended to be prescriptions for individual treatment. Specific therapy should be tailored to the needs and circumstances of individual patients. Pharmacologic therapy must be accompanied at every step by patient education and measures to control those factors that contribute to the severity of the asthma (see components 2 and 4).

If optimal control of asthma is not achieved and sustained at any step of care (nocturnal symptoms, urgent care visits, or an increased need for short-acting beta$_2$-agonists are key indications that asthma is not optimally controlled), several actions may be considered:

- Patient adherence and technique in using medications correctly should be assessed.
- A temporary increase in anti-inflammatory therapy may be indicated to reestablish control. A deterioration of asthma may be characterized by gradual reduction in PEF (approximately 20 percent), by failure of inhaled bronchodilators to produce a sustained response, by a reduced tolerance to activities or exercise, and by the development of increasing nocturnal symptoms. To regain control of asthma, a short course of oral prednisone (see figure 3-5a) is often effective. If asthma symptoms do not recur and pulmonary functions remain normal, no additional therapy is necessary. However, if the prednisone burst does not control symptoms, is effective only for a short period of time (e.g., less than 1 to 2 weeks), or is repeated frequently, the patient should be managed according to the next higher step of care.
- Other factors that diminish control may need to be identified and addressed. These factors include the presence of a coexisting condition (e.g., sinusitis), a new or increased exposure to allergens or irritants, patient or family barriers to adequate self-management behaviors, or psychosocial problems. In some cases, alternative diagnoses may need to be considered, such as vocal cord dysfunction.
- A step up to the next higher step of care may be necessary.
- Consultation with an asthma specialist may be indicated (see component 1-Initial Assessment and Diagnosis).

Intermittent Asthma

Step 1: Mild Intermittent Asthma. Short-acting inhaled beta$_2$-agonists taken as needed to treat symptoms are usually sufficient therapy for mild, intermittent asthma. If effective in relieving symptoms and normalizing pulmonary function, intermittent use of short-acting inhaled beta$_2$-agonists can continue to be used on an as-needed basis. If significant symptoms reoccur or beta$_2$-agonist is required for quick-relief treatment more than two times a week (with the exception of using beta$_2$-agonist for exacerbations caused by viral infections and for exercise-induced bronchospasm [EIB]), the patient should be moved to the next step of care.

Patients with intermittent asthma who experience EIB benefit from taking inhaled beta$_2$-agonists, cromolyn, or nedocromil shortly before exercise (see Exercise-Induced Bronchospasm, page 100). Cromolyn or nedocromil taken before unavoidable exposure to an aeroallergen known to exacerbate the patient's asthma may be beneficial (Cockcroft and Murdock 1987).

The Expert Panel recommends the following actions for managing exacerbations due to viral respiratory infections, which are especially common in children. If the symptoms are mild, inhaled beta$_2$-agonist (every 4 to 6 hours for 24 hours, longer with a physician consult) may be sufficient to control symptoms and improve lung function. If this therapy needs to be repeated more frequently than every 6 weeks, a step up in long-term care is recommended. If the viral respiratory infection provokes a moderate-to-severe exacerbation, a short course of systemic corticosteroids should be considered. For those patients with a history of severe exacerbations with viral respiratory infections, systemic corticosteroids should be initiated at the first sign of the infection.

The Expert Panel recommends that a detailed written action plan be developed for those patients with intermittent asthma who have a history of severe exacerbations (see figure 4-5). Intermittent asthma—infrequent exacerbations separated by periods of no symptoms and normal pulmonary function—is often mild. However, some patients with intermittent asthma experience sudden, severe, and life-threatening exacerbations. It is essential to treat these exacerbations accordingly. The patient's action plan should include indicators of worsening asthma (specific symptoms and PEF mea-

surements), as well as specific recommendations for using beta$_2$-agonist rescue therapy, early administration of systemic corticosteroids, and seeking medical care. Furthermore, periodic monitoring (see component 1-Periodic Assessment and Monitoring) of the patient is appropriate to evaluate whether the patient's asthma is indeed intermittent or whether a step up in long-term therapy is warranted.

Persistent Asthma

The Expert Panel recommends that patients with persistent asthma, either mild, moderate, or severe, receive daily long-term-control medication. The most effective long-term-control medications are those with anti-inflammatory effects, that is, those that diminish chronic airway inflammation and airway hyperresponsiveness. Evidence from clinical trials supports this recommendation (van Essen-Zandvliet et al. 1992; Kerstjens et al. 1992).

Step 2: Mild Persistent Asthma. The main characteristics of step 2 care are as follows:

- Step 2 care long-term-control medication is daily anti-inflammatory medication: either inhaled corticosteroids at a low dose (see figure 3-5b), cromolyn, or nedocromil. For children, a trial of cromolyn or nedocromil is often the initial long-term therapy due to the safety profiles of these medications.

- Sustained-release theophylline is an alternative, but not preferred, long-term-control medication. It is not preferred because its modest clinical effectiveness (theophylline is primarily a bronchodilator and its anti-inflammatory activity demonstrated thus far is modest) must be balanced against concerns about potential toxicity (see component 3-Medications). Theophylline remains a therapeutic option for certain patients due to expense or need for tablet-form medication.

  Sustained-release theophylline is given to achieve a serum concentration of between 5 and 15 mcg/mL. Periodic theophylline monitoring is necessary to maintain a therapeutic—but not toxic—level.

- Zafirlukast or zileuton may also be considered an alternative long-term-control medication for patients 12 years of age and older, although their position in therapy is not yet fully established. Initial experience in clinical trials and possible patient requirements for tablet-form medication make these new medications a therapeutic option. Further clinical experience and additional data are needed to establish the role of zafirlukast and zileuton in stepwise therapy.

- Quick-relief medication must be available. Inhaled short-acting beta$_2$-agonists should be taken as needed to relieve symptoms. The intensity of treatment will depend on the severity of the exacerbation (see component 3-Managing Exacerbations). Use of inhaled short-acting beta$_2$-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.

Step 3: Moderate Persistent Asthma. Consultation with an asthma specialist may be considered because the therapeutic options at this juncture pose a number of challenging risk/benefit outcomes. There are at least three options for initiating step 3 therapy:

- Increase inhaled corticosteroids to medium dose. This strategy will benefit many patients. Adverse effects, although infrequent, may arise (see component 3-Medications).

OR

- Add a long-acting bronchodilator to a low-to-medium dose of inhaled corticosteroids. The long-acting bronchodilator may be either a long-acting inhaled beta$_2$-agonist (e.g., salmeterol) (Greening et al. 1994; Woolcock et al. 1996) or sustained-release theophylline (Nassif et al. 1981); although not preferred, long-acting beta$_2$-agonist tablets may be considered. This approach has been shown to improve symptom control and may be especially beneficial in patients who have significant nocturnal symptoms. Improved asthma control has been demonstrated with an inhaled long-acting beta$_2$-agonist and a medium-dose inhaled corticosteroid compared to a doubled dose of inhaled corticosteroid (Woolcock et al. 1996), but the potential for incorrectly using long-acting inhaled beta$_2$-agonists as a quick-relief medication needs to be considered. The approach of adding theophylline has the potential for adverse reactions related to fluctuations in theophylline serum concentrations.

OR

- Establish control with medium-dose inhaled corticosteroids, then lower the dose (but still within the medium-dose range) and add nedocromil. Nedocromil has a notable safety profile, and some studies (Lai et al. 1993; O'Hickey and Rees 1994; Svendsen and Jorgensen 1991) have shown that it has some, albeit modest, inhaled corticosteroid-sparing effects in adults. Other studies (e.g., Wong et al. 1993) did not demonstrate this. Therefore, this treatment option is not preferred. Furthermore, adding another inhaler into the patient's medication schedule may affect patient adherence. It will also affect the total cost of care.

If the patient's asthma is not optimally controlled with initial step 3 therapy, and medications are used correctly, additional step 3 therapy is recommended.

- Increase daily long-term-control medications to a high dose of inhaled corticosteroids,

AND

- Add a long-acting bronchodilator, especially to control nocturnal symptoms. The long-acting bronchodilator can be either long-acting inhaled beta$_2$-agonist or sustained-release theophylline. An evening dose of either bronchodilator may alleviate and prevent nocturnal symptoms and thus improve adherence to the overall therapeutic regimen.

Step 4: Severe Persistent Asthma. Patients whose asthma is not controlled on high doses of inhaled corticosteroids and the addition of long-acting bronchodilators will also need oral systemic corticosteroids on a regularly scheduled, long-term basis. For patients who require long-term systemic corticosteroids:

- Use the lowest possible dose (single dose daily or on alternate days).
- Monitor patients closely for corticosteroid adverse side effects (see component 3-Medications).
- When control of asthma is achieved, make persistent attempts to reduce systemic corticosteroids. High doses of inhaled corticosteroids are preferable to systemic corticosteroids because inhaled corticosteroids have fewer systemic effects.
- Consultation with an asthma specialist is recommended.

SPECIAL CONSIDERATIONS FOR MANAGING ASTHMA IN DIFFERENT AGE GROUPS

Infants and Young Children (5 Years of Age and Younger)

KEY RECOMMENDATIONS FOR MANAGING ASTHMA IN INFANTS AND YOUNG CHILDREN

- Diagnosing asthma in infants is often difficult, yet underdiagnosis and undertreatment are key problems in this age group. Thus, a diagnostic trial of inhaled bronchodilators and anti-inflammatory medications may be helpful.
- In general, infants and young children consistently requiring symptomatic treatment more than two times per week should be given daily anti-inflammatory therapy.
- When initiating daily anti-inflammatory therapy, a trial of cromolyn or nedocromil is often given due to the safety profile of these medications.
- Response to therapy should be carefully monitored. Once control of asthma symptoms is established and sustained, a careful step down in therapy should be attempted. If clear benefit is not observed, alternative therapies or diagnoses should be considered.

Diagnosis

Several studies show that as many as 50 to 80 percent of children with asthma develop symptoms before their fifth birthday. Diagnosis can be difficult in this age group and has important implications. On the one hand, asthma in early childhood is frequently underdiagnosed (receiving such labels as chronic bronchitis, wheezy bronchitis, recurrent pneumonia, gastroesophageal reflux, and recurrent upper respiratory tract infections), and thus many infants and young children do not receive adequate therapy. On the other hand, not all wheeze and cough are caused by asthma, and caution is needed to avoid giving infants and young children inappropriately prolonged asthma therapy. Episodic or